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AN ANALYSIS OF THIRTY CONSECUTIVE CASES OF ALLERGIC CONJUNCTIVITIS

J. WARRICK THOMAS, M.D. and W. A. WARREN, M.D.

Review and History

The question of allergic conjunctivitis dates back to the year 1796, at which time Edward Jenner vaccinated for smallpox successfully. Many other workers have contributed to this subject. Among the more prominent ones are Magendie and Pasteur, and in recent years such workers as Wilmer and Woods. There is no need to go into a resumé of the etiology and contributions, as Hansel has made a very complete and adequate report of these observations[1].

The present series of cases consists of consecutive patients in which a diagnosis of allergic conjunctivitis was made. In addition, these cases have had an adequate allergic investigation. Approximately 90 per cent of these patients were seen by Dr. A. D. Ruedemann of the Department of Ophthalmology, and he has concurred in the diagnosis of an allergic conjunctivitis. A large number of these cases were referred to us by him for study from the point of view of allergy as a possible factor in their presenting problem. These patients were treated locally only in certain isolated instances, according to recommendations made by the Eye Department. In the majority of cases, all local medication was discontinued. Also, possible contact factors such as cosmetics, and exposure to various inhalants, for example, dust, feathers, etc., were eliminated.

Out of thirty cases, nine of these patients were in the third decade of life. It was interesting to observe that there was an equal distribution of cases in the first, second, fifth, sixth and seventh decades (three patients in each decade). (See fig. 1.)

SEASONAL EXACERBATION OF SYMPTOMS

Four of the thirty cases showed seasonal variations of their conjunctivitis, and two of this group also had perennial symptoms, but with definite seasonal exacerbations. One patient had trouble only during the summer months. The second patient had symptoms only during the fall of the year, especially during the ragweed season and had, in addition to his allergic conjunctivitis, a perennial and seasonal allergic rhinitis, migraine, food allergy and bronchial asthma. The seasonal symptoms were entirely controlled by ragweed therapy. His conjunctivitis was due to molds and inhalants most likely, as he gave very strong reactions to dust, orris root, and slight reactions to other of the common inhalants and strong, definite reactions to seven different molds to which he was tested. On a program of hyposensitization he showed a definite and steady improvement of his symptoms. He is not having any trouble with his eyes

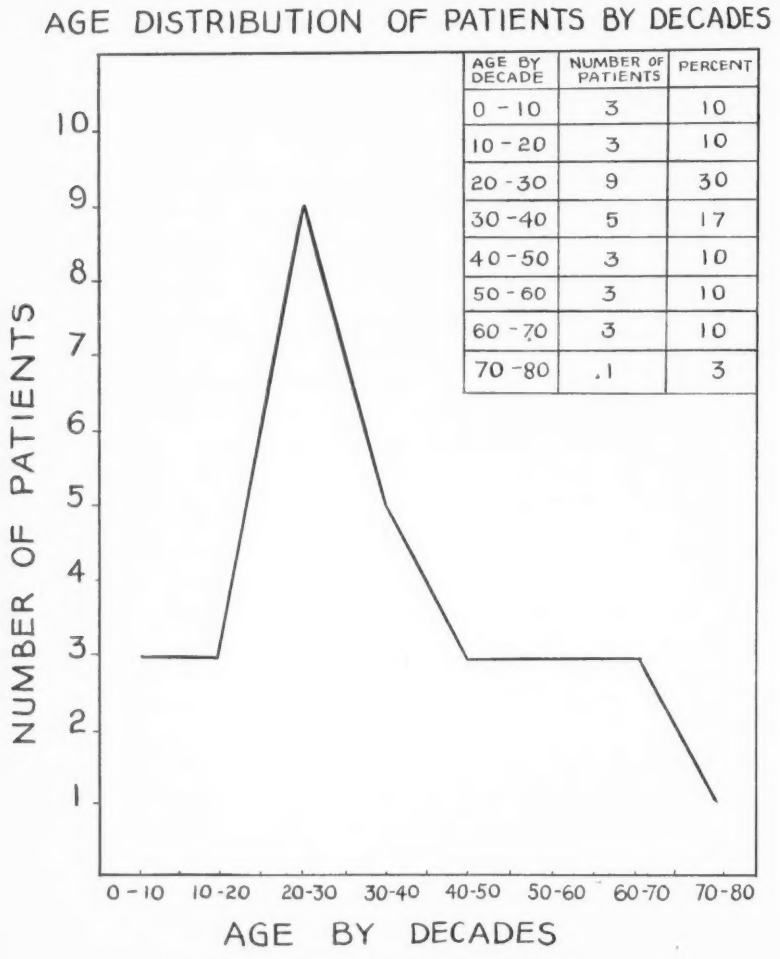

FIGURE 1: Age distribution of patients by decades.

at this time, although the air contains a moderate pollen count (150).

The second case is that of a student who had symptoms throughout the year, with a definite flare-up with his eyes during the summer months, especially during June and July. He too gave very strong reactions to a large number of the common inhalants and to a number of the molds. He gave positive scratch reactions to house dust and cat and dog hair, and positive scratch reactions to alternaria and monilia. He had a seasonal hay fever (fall) in addition to his allergic conjunctivitis. His symptoms were so severe at the time of his original studies that he had some difficulty in carrying on his school work. Since the onset of the ragweed sea-

son he has not experienced any symptoms of hay fever. He received preseasonal ragweed hyposensitization and we attempted to desensitize him to the inhalants and molds to which he reacted. He reported that he has had excellent results with no symptoms during the past seven months.

Another patient (case No. 26) had a vernal conjunctivitis with characteristic cobblestone lesions which was entirely seasonal, in addition to an atopic dermatitis, perennial allergic rhinitis and chronic urticaria. Her first symptoms developed on May 1, 1938, and continued until September 1, 1938. The second attack started April, 1939, and was similar to the previous attack, but more severe. She had a marked photophobia, and found it necessary to use many different types of eye drops in order to gain any relief. This patient gave very strong reactions to the common inhalants and molds. She has had fair results on a program of hyposensitization and dietary restrictions, eliminating especially those foods to which she gave a strong reaction (two or three plus).

At one time during the program of treatment, after her eyes had improved, she started having a flare-up of symptoms after taking 0.5 cc. of an extract containing dust, orris root, mattress dust, tobacco smoke and ashes 1:1,000, silk 1:5,000 and a second extract containing a mixture of the molds 1:1,000 and oidiomycin 1:10,000. This was controlled to some extent by a reduction of the dosage of extract.

The fourth patient having a pure seasonal allergic conjunctivitis was a lad nine years of age who had had recurrent attacks of vernal catarrh

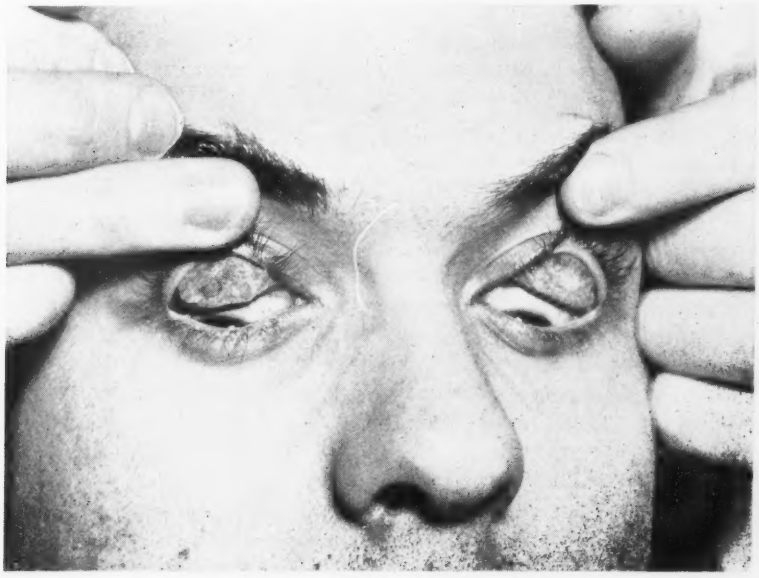

FIGURE 2: Typical cobblestone lesions seen in vernal catarrh.

during the past four years, coming on each spring and lasting several months. Last year was the first time that his conjunctivitis continued until frost. At the time that he was originally observed here at the Clinic he had marked ulcerations of the cornea, and typical cobblestone lesions (see figure 2) on the inner surfaces of the lids. He gave negative reactions to all of the pollens by the scratch method and by Ophthalmo test (grasses, ragweed and trees). He gave only moderate reactions to the inhalants and molds and was placed on a program of hyposensitization against dust, tobacco smoke and ashes, and a mixture of the molds. He was also restricted in diet and was seen at five-week intervals. He had recurrent flare-ups until the dosage of the extract was stabilized. He was last observed on September 16, 1939, and his eyes had entirely cleared up, with the disappearance of the characteristic cobblestone lesions and corneal ulcerations. His parents reported that he had been "getting along fine" and that he had gained some eight pounds in weight during the summer months. They stated that during a similar period of time last year, his symptoms were most pronounced.

Etiological Agents Suspected by the Patients

The patients were questioned as to the possible causative agents or factors that they themselves felt might be related to their presenting symptoms. These were classified under the headings of (1) inhalant factors including dust, feathers, orris root, silk, molds, etc., (2) foods, (3) chemicals, such as paints, fumes, drugs and cosmetics, and (4) physical or climatic factors such as wind, bright lights, sunshine, heat and cold. Fourteen patients, or forty-seven per cent, felt that inhalants were responsible for their symptoms.

Case No. 18 reported for study three weeks after the onset of his symptoms, the latter part of May, 1939. He complained of stabbing pains in his eye and stated that at the time of onset of his symptoms he had been cleaning some old books and records in the office and was covered with dust. He had had fall hay fever up until four years ago. Since that time, his symptoms have been controlled by ragweed hyposensitization. He has had in the past some bronchial asthma (seasonal) and a possible food allergy. He gave significant and strong reactions to the common inhalants and strong reactions to the molds. He was placed on a program of hyposensitization against the inhalants and molds along with his preseasonal ragweed treatments. Certain foods to which he gave severe reactions were eliminated from his diet. He has responded nicely to treatment and has obtained excellent results.

Five patients felt that foods were definitely related to the exacerbation of their symptoms. Of this five, two knew definitely which foods caused them trouble. One patient, case No. 14, thought that foods might be a factor, but was unable to state any definite food as being responsible for

TABLE 1

	ALLIED ALLERGIC CONDITIONS									OTHER ALLERGIC (?) OCULAR DISORDERS					
Patient Number	*Asthma*	*Asthmatic Bronchitis*	*Perennial Allergic Rhinitis*	*Hay-fever*	*Atopic Dermatitis*	*Urticaria and A.N.E.*	*G. I. Allergy*	*Migraine*	*Misc.*	*Recurrent Styes*	*Contact Derm. Lids*	*Chronic Meibomianitis*	*Vernal Catarrh*	*Herpetic Keratitis*	*Phlyctenular Keratoconjunctivitis*
1			+				+								
2															
3			+												
4															
5															
6															
7			+	+											
8			+	+						+					
9			+				+	+							
10		+	+						+ (b)						
11			+											+	
12			+												
13															
14		+	+												
15															
16															
17			+								+				
18	+ (a)	+ (a)	+	+			+	+							
19				+						+					
20			+				+								
21												+			
22	+ (a)			+											
23							+								+
24		+	+					+					+		
25			+												
26			+		+	+							+		
27			+												
28			+			+							+		
29					+										
30			+						+ (c)		+				

a. Seasonal. b. Laryngitis.
c. Contact dermatitis.

The instance of the various allergic manifestations or allied allergic conditions in addition to the diagnosis of an allergic conjunctivitis.

her eye symptoms. She did feel that she had experienced a definite exacerbation of symptoms usually in the evening, after supper.

One little patient, four and a half years of age, (case No. 23) has had recurrent conjunctivitis and gastro-intestinal symptoms. The mother questioned whether some foods might be related to the "ulcers in the eyes." She further went on to state that following the use of atropine the child had had some atropine dermatitis. This was confirmed by the referring physician who said she was also slightly susceptible to scopolamine.

A man (case No. 7), aged twenty-one, stated definitely that he had an exacerbation of his symptoms following the ingestion of cantaloupe. Another patient (case No. 29) experienced an exacerbation of symptoms following the ingestion of strawberries. In addition to the conjunctivitis, she had a contact dermatitis caused by using certain creams and lotions on her hands, which cleared up entirely following elimination of the offender.

One patient (case No. 1) had an increase of eye symptoms following the ingestion of eggs. This patient also had an associated genito-urinary allergy, characterized by paroxysmal nocturia following the ingestion of eggs. On the elimination of eggs from his diet, the nocturia cleared up and has not recurred. He has had some continuation of eye symptoms since that time, and we felt that although the eye symptoms may be related to the ingestion of eggs, there were other factors which have to be considered. His genito-urinary symptoms were so pronounced that he has refused to eat eggs again.

Five patients stated that they had a definite conjunctivitis following contact with chemical agents. Fresh paint in two instances (cases No. 1 and No. 16) caused symptoms. Another patient (case No. 17) found that during the time that she was using a certain washing powder, her eye symptoms were always increased. A young lady (case No. 30) experienced a definite flare-up of her conjunctivitis after using mascara on several successive nights. She stated that occasionally she could use this preparation for one night only without any exacerbation of symptoms but that she was unable to use it continuously as she always experienced trouble after three or four days' use.

A man (case No. 27), thirty-nine years old, found that following the taking of aspirin he experienced an exacerbation of his conjunctivitis. This cleared up after the drug was eliminated. In addition, he observed intense redness and itching following the use of a feather pillow. This was controlled by the use of an Allergen-Proof Pillow encasing.

Under the miscellaneous causes, six patients felt that certain physical factors caused them trouble. Of this six, four experienced a definite

conjunctivitis following exposure to wind. Two of the group had an increase of symptoms after exposure to bright lights or sunshine.

A Comparison of the Results of Skin Tests with the Suspected Etiological Agents

Results of skin tests concurred with the history of inhalant factors responsible for eye symptoms in 14 cases. Significant skin tests were found in three cases out of five in which foods were suspected. Positive patch tests were found in two instances where contact factors were suspected.

The entire group of patients was tested with stock bacteria consisting of vaccines made from nine different varieties of organisms. Fifty per cent of the cases studied gave very strong bacterial reactions, more so than one usually finds in the routine study of allergic individuals. We have not drawn any definite conclusions from this, but report it as a possible coincidental factor.

Other Related Allergic Manifestations

Only six of the thirty cases, or 20 per cent, had no related allergic manifestations. Seven of the patients had, in addition to their conjunctivitis, one additional allergic manifestation. Nine had two other allergic manifestations. Seven cases had three or more other allergic conditions with their conjunctivitis. (See table No. 1.)

One-third of the cases studied gave a history of one or more previous allergic manifestations which they had not experienced during recent months.

Results of Treatment

These patients were observed over a period of time from two months to four years and eight months. One-half of the cases were observed for six months or longer, and the rest were observed over a period of two to six months.

Our results of treatment were classified under the following headings: excellent, good, fair, poor, no report, not treated.

From the reports of the results of treatment to date, we have experienced satisfactory results in over fifty per cent of these patients. This group of patients was not selected, but consists of thirty consecutive cases of allergic conjunctivitis with no exceptions.

Reference

1. Hansel, French K.: "Allergy of Nose and Paranasal Sinuses". C. V. Mosby Co., St. Louis, 1936.

SUBACUTE MENINGOMYELITIS SIMULATING SPINAL CORD TUMOR

Report of a Case

A. T. Bunts, M.D.

Inasmuch as surgery is the primary form of treatment of spinal cord tumors, but is definitely contraindicated in the presence of inflammatory or degenerative lesions of the cord, it seems worthwhile to review the case of a patient who died soon after a laminectomy for suspected spinal cord tumor. This clinical diagnosis proved to be wrong, and post-mortem examination revealed a definite subacute meningomyelitis. The operation undoubtedly hastened the patient's death, and for that reason, in spite of the apparent justifiability of laminectomy as viewed in retrospect, the clinical features of the case deserve a searching analysis in order to determine if possible the reasons for the erroneous diagnosis and thus to avoid surgery in similar cases in the future.

Case Report

Chief complaint—The patient, a 53 year old white housewife, who had been in previous good health except for menopausal symptoms, stated that during the year prior to coming to the Clinic she had experienced occasional pain between the shoulder blades radiating around the chest to its anterior aspect. The pain was more noticeable at night. No other symptoms were noted until eleven weeks before entrance to the Clinic, when she felt a sudden pain in the lower back while stooping over; this pain lasted for two or three days. During the next two weeks her legs gradually became numb and stiff, more markedly so on the right side. She began to stumble and fall when she walked, she was unable to feel a hypodermic needle in her leg, and she burned her right leg without realizing it. The numbness of the legs gradually extended up the trunk to the arms and there was an "itchy" sensation across the breasts. Six weeks before entering the Clinic the patient lost control of the vesical and rectal sphincters. There was no history of fever or headache during the present illness.

Family history and past history were irrelevant to the present condition. There was no history of tuberculosis, influenza, or other infectious disease prior to the onset of the present illness.

General physical examination revealed a slender adult white woman in no apparent distress, perfectly conscious and cooperative. Temperature 98.6° F. Pulse rate 100 and regular. Blood pressure 120/84. There was no evidence of pulmonary, cardiac, or intra-abdominal disease.

***Neurological examination.** There was practically complete anesthesia below the fourth thoracic dermatome. Both legs were very weak, the right leg more so than the left leg. Abdominal reflexes were absent.*

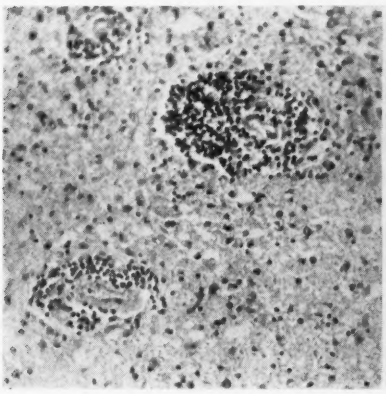

FIGURE 2: Photomicrograph of section from eighth cervical segment of spinal cord showing marked necrosis of the grey matter and extensive perivascular and parenchymatous infiltration with round cells. Hematoxylin and eosin stain. (x 150).

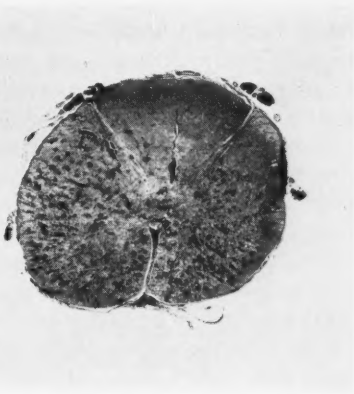

FIGURE 1: Section from eighth cervical segment of spinal cord showing degeneration of the long fiber tracts and extensive perivascular infiltration. Weigert myelin sheath stain.

Both patellar reflexes were hyperactive and there was a positive Babinski sign on both sides. The rectal sphincter was relaxed.

***Roentgen examination** of the thoracic spine showed no abnormal change.*

***Laboratory data.** Urinalysis was negative except for a trace of albumin; red blood cells 5,550,000; white blood cells 6000; hemoglobin 91 per cent; blood sugar 95 mgm. per cent; and blood Wassermann and Kahn reactions were negative.*

***Lumbar puncture** showed clear, colorless cerebrospinal fluid at an initial pressure of 130 mm. of water. There were no arterial pulsations in the column of fluid. The Queckenstedt test showed a very slow rise of the fluid level during jugular compression and a slower fall on release of jugular compression. These dynamic studies definitely indicated a partial spinal subarachnoid block.*

***Examination of the cerebrospinal fluid** revealed a cell count of 22 lymphocytes per cubic millimeter, globulin negative, total protein content 275 mgm. per 100 cc., Wassermann reaction negative, colloidal gold reaction negative. No culture or smear of the fluid was made.*

***A tentative diagnosis** of spinal cord compression at the fourth thoracic segment by an extramedullary tumor was made.*

One cubic centimeter of heavy lipiodol was injected into the cisterna magna and it failed to descend in the spinal subarachnoid space below the level of the third cervical vertebra.

***Operation.** Laminectomy was carried out from the third cervical*

vertebra to the second thoracic vertebra inclusive. The dura appeared to be normal and when it was opened in the midline and held aside with traction sutures throughout the length of the exposure, there was found to be practically no cerebrospinal fluid in the subarachnoid space. There were numerous adhesions between the arachnoid and the pia and between the arachnoid and the dura throughout the exposure. Many of the pia-arachnoidal adhesions were separated by means of forceps, and high up beneath the first and second cervical vertebrae the cerebrospinal fluid appeared to be imprisoned in loculations or adhesions of the arachnoid. After freeing some of the adhesions, a small amount of fluid together with globules of lipiodol escaped. The arteries of the upper cervical cord appeared to be somewhat dilated and engorged. At the level of the eighth cervical and first thoracic segments, the cord was enlarged in fusiform fashion and filled the canal; there was no vascular engorgement at that level. No extramedullary tumor was found at any level of the exposure. Because it was thought that the fusiform swelling of the cord might be due to an intramedullary tumor or a cystic cavity, a hypodermic needle on a syringe was inserted through the posterior columns of the cord, but no fluid was obtained by aspiration. It was the operator's final impression that he was probably dealing with a meningomyelitis and that the adhesions which obstructed the free flow of cerebrospinal fluid in the subarachnoid space had been the cause of the partial block by Queckenstedt's test. The wound was closed, and because of the patient's low blood pressure at the end of the operation she was given a transfusion of 500 cc. of whole blood.

Postoperative course. *The patient did not react properly after operation and her blood pressure remained very low in spite of stimulation with caffeine and ephedrine and venoclysis. Because of periods of apnea the patient was placed in an oxygen tent. During the day after operation there was a gradually progressive cardiorespiratory failure, which failed to respond to any form of treatment, and the patient expired thirty-five hours after operation.*

Post-mortem examination. *The external surface of the brain appeared to be grossly normal and showed no evidence of meningitis. Gross transverse sections of the brain showed no abnormal changes. The entire spinal cord was removed and it presented some interesting features. At the level of the eighth cervical and first thoracic segments there was a well-marked, diffuse swelling of the cord which was soft in consistency. A transverse section of the cord at this level showed necrosis and a small area of hemorrhage about the central canal. The lumbar portion of the cord was much narrower than normally and presented an atrophic appearance. There were numerous adhesions between the arachnoid and the cord throughout its length. Microscopic examination of the cord at the eighth cervical and first thoracic segments showed necrosis of the cord and*

extensive round cell infiltration in the perivascular spaces and in the meninges. The lower thoracic and lumbar segments of the cord also showed a similar round cell infiltration, but no extensive necrosis. No organisms were found in the sections and special stains for tubercle bacilli revealed none. Gross and microscopic examination of the cord failed to disclose a tumor of either the extramedullary or intramedullary type. Examination of the thoracic and abdominal organs showed only congestion and edema of the lungs, congestion of the liver, spleen and kidneys, and fibroids of the uterus.

Final pathological diagnosis: *Subacute meningomyelitis of unknown origin.*

Greenfield and Turner[1], reporting three cases similar to the above case, have given an excellent description of their clinical and pathological features.

Discussion

In reviewing the history of the patient's illness, one is impressed by the initial symptom of interscapular pain radiating around the chest. This suggests "root pain" which is often the first symptom of extramedullary tumor. The afebrile course of the disorder and the gradual development of numbness and weakness of the legs, numbness of the trunk and arms, and loss of sphincter control, together with the sensory level and pyramidal tract signs found on examination are entirely consistent with a diagnosis of spinal cord compression. Complete or partial spinal subarachnoid block and elevation in the total protein content of the cerebrospinal fluid obtained by lumbar puncture are present in approximately 90 per cent of cases of spinal cord tumor, so that similar findings in this case appeared to be additional evidence in favor of such a lesion.

In the face of what appeared to be overwhelming evidence in favor of the presence of a spinal cord tumor, the important diagnostic finding of 22 cells per cubic millimeter in the cerebrospinal fluid was disregarded. For practical purposes, normal cerebrospinal fluid may be considered to contain not more than 5 cells per cubic millimeter, according to Merritt and Fremont-Smith[2]. The same authors[3], reviewing the findings in 36 cases of tumor in the spinal canal, found that the cell count was normal in two-thirds of the fluids and was greater than 25 per cubic millimeter in only five. The highest cell counts in their series were 78 and 90 in patients with meningiomas. In a series of 36 spinal cord tumors at the Cleveland Clinic, analyzed five years ago, the cell count in the cerebrospinal fluid was below five in 89 per cent of the cases and never above 17. A cell count of 22 per cubic millimeter of cerebrospinal fluid is definitely abnormal, and in the case which has been presented, it was the only finding which seemed out of place in the convincing clinical picture of

spinal cord tumor. It now seems clear that an abnormally high cell count in the cerebrospinal fluid, even though of very moderate degree, should cause one to hesitate before making a diagnosis of spinal cord tumor and before advising operation. At least it might be justifiable to try the effect of some nonsurgical form of therapy before resorting to laminectomy. Roentgen therapy, which has proved beneficial in some cases of acute and subacute encephalitis, should be given a trial in selected cases of nontuberculous and nonsyphilitic inflammatory disease of the spinal cord, particularly in those cases which present a lymphocytic pleocytosis in the cerebrospinal fluid.

References

1. Greenfield, J. C. and Aldren Turner, J. W.: Acute and subacute necrotic myelitis, Brain, 62:227-252, (September) 1939.
2. Merritt, H. H. and Fremont-Smith, F.: The Cerebrospinal Fluid, W. B. Saunders Co., Philadelphia (1937), p. 57.
3. Ibid, p. 171.

RADIATIONS EMITTED BY LIVING ORGANISMS

By Dr. Otto Glasser

According to our present knowledge, three different ranges of radiations are emitted from living organisms. These ranges can be classified according to their wave lengths or their place in the general electromagnetic spectrum. First, practically all organisms emit infra-red radiation, the wave length of which depends, as far as we know, entirely upon the temperature of the body. The second group of radiations belongs to the visible range of the spectrum; these radiations are produced by bio-luminescent phenomena. This emission of visible light by living organisms has been known for a long time. Ever since the great philosopher Aristotle mentioned the light emitted by certain fish, this so-called "cold light" has held the interest of biologists, physicists, and chemists. Many organisms in both the animal and the plant kingdoms are bio-luminescent, the best known being the firefly, the glowworm, and luminescent bacteria. Though bio-luminescent radiations can be satisfactorily analyzed as far as their spectral distribution is concerned, we know as yet very little about the way in which they are produced. Fundamentally speaking, certain substances formed within the cell are oxidized, but neither the composition of these substances nor the essential processes of their oxidation are known.

The third group of biologic radiations, the so-called mitogenetic rays, are perhaps of greatest interest to medicine. Emission of mitogenetic radiation, according to their discoverer, Alexander Gurwitsch[1], a Leningrad histologist, is universally connected with growth in general and notably the process of mitosis of cells. Cell division had been studied widely in the past before Gurwitsch's experiments, but there were certain inexplicable phenomena which did not fit into the various theories proposed. For instance, an often observed increased mitosis caused by the stimulus of an unknown exogen factor was never satisfactorily explained. One such example was the "regeneration mitosis" occurring around damaged tissues. Neighboring tissues attempted to repair the damage and consequently an increased rate of cell division around the damaged tissue occurred. It is on this point that Gurwitsch's experiments and theories hinge. In one experiment, he inflicted a small wound on the corneal epithelium of a frog's eye. The eye tissues were later removed and stained and it was found that the areas surrounding the wound contained many more mitotic figures than the unaffected regions. The simultaneous production of an additional wound in the neighborhood of the first wound caused peculiar distribution of the mitotic changes. The second wound acted as a barrier to the stimulus emanating from the first wound.

Gurwitsch concluded from this experiment that the stimulus must be

oscillatory in character and that probably a "mitogenetic radiation" emitted from the original wound was responsible for the effect. Gurwitsch[2] proceeded on this hypothesis and tried to learn first whether this radiation could also be transmitted through space and not only within the tissues. Most of his earlier experiments were conducted with onion roots, the actively growing end portion of which was selected as the most suitable place for determining the effect of a stimulus to cell division. This onion experiment, which became the foundation of all later work on problems of mitogenetic radiation, was performed with two onion roots, one serving as a "sender," the other as a "detector" of the stimulating radiation. When, after the exposure, the induced region of the detector root was examined histologically, it was always found that there was an increase in the number of mitotic figures on the side exposed to the sender root. A stimulating effect had been exerted through space without direct contact. This cause of a stimulation through space was found to pass easily through quartz but was stopped by glass. Gurwitsch therefore concluded that the stimulation was of a wave character and that its wave length lay in the ultraviolet region of the spectrum, around 2000 Angström units (2000 times 10^{-8} centimeters).

Following Gurwitsch's original publications, numerous investigations have been conducted to study the various aspects of the phenomena, biological, chemical, and physical[3]. Among the many biologic experiments, the studies on the sensitivity of amitotically reproducing organisms such as beer yeast to mitogenetic radiations which were carried out by Baron in 1926, have led to the most important results. In the yeast organisms, an increasing rate of budding of yeast cells with a subsequent increase in the total number of individual cells was observed after exposure to mitogenetic senders such as the onion root. The yeast method subsequently replaced almost entirely the more laborious methods of preparing onion root sections and counting mitoses.

We have felt for over ten years that if Gurwitsch's fundamental experiments and theories could be confirmed they would be of immense value to the clinician in studying many medical problems. We therefore proceeded to study the mitogenetic problem and among other methods we used a modification of Baron's original yeast method to detect mitogenetic radiation. Our modification of this method may be described shortly[4]. Pure cultures of Saccharomyces cerevisiae and ellipsoideus in liquid beer-wort and a peptone glucose medium were used. Equal quantities, 0.5 to 2.5 cc. of this yeast suspension were measured accurately into quartz and glass test tubes. The lower ends of the test tubes were then placed in direct contact with the various biological radiators and rotated continuously but slowly during the irradiation in order to prevent settling of the yeast. After the irradiation, the tubes were placed in an incubator and kept at 20° C. for periods up to 24

hours. Then sulfuric acid was added to kill the yeast cells and after the tubes were thoroughly shaken, the amount of yeast present was determined in the following way: The suspensions were introduced into small hematocrit tubes which were rotated rapidly in the centrifuge for five minutes. The height of the packed yeast cell columns in the hematocrit tubes which had previously been calibrated carefully was then determined and the percentage difference between the columns of cells irradiated in the quartz tube and the glass tube were calculated. With this method, the emission of radiation from various biological tissues (notably rat cancer) and organs was studied.

Later on this method was revised after receipt of further information and also of two strains of yeast from the laboratories of Gurwitsch in Leningrad[5]. Cultures of this yeast were prepared in strict conformity with the procedure outlined by Gurwitsch. The agar beer-wort cultures were homogeneous at the time of exposure and could be detected only microscopically. After a period of incubation not exceeding two hours, the yeast was gently removed with a loop, fixed on a glass slide, and stained with methylene blue. The percentage of small buds was then counted in groups of 1000 unselected cells. The Russian workers advised that an increase in buds was more directly related to the mitogenetic effect than increasing volume. Again biological, chemical, and physical "senders" were used for the radiation of the yeast. With a few exceptions our results did not substantiate those of Gurwitsch and his co-workers.

Gurwitsch's conclusions may be summarized briefly: Mitogenetic radiation has been found to be given off by simple organisms, bacteria, and yeasts; by plant tissues; by embryonal animal tissues; by skeletal and cardiac muscle in contraction; by nerve fibers, spleen, corneal ciliated and gut epithelia, by blood and urine, and by tumors.

The study of tumor tissue is of special interest since the radiation from malignant tumors is said to be stronger than that from benign tumors. Moreover, in cancerous conditions, Gurwitsch maintains that normally appearing blood radiation is absent. These properties peculiar to tumors suggest the possibility of utilizing the methods of mitogenetic study for the early diagnosis of cancer.

Naturally these observations called the attention of the whole medical world to the great importance of using the Gurwitsch effect for early diagnosis in certain disease and it is for this reason that a large number of investigators devoted their time to a thorough study of the problem. We, like many others, turned our attention to the construction of physical detectors for the radiation in order to avoid the complications often inherent in biological methods. We first employed photographic methods to detect mitogenetic radiation and later resorted to the photoelectric Geiger-Mueller counter tube[6]. We soon had to abandon the

photographic method as being unreliable. The various Geiger counters which we built and with which we experimented were described in previous communications[4,7,8]. In brief, they consisted of cylindrical quartz tubes containing a photo-electric electrode and central tungsten wire anode. They were connected through a multi-stage vacuum tube amplifier to a magnetic counter or a loud speaker. The photo-sensitive materials which we mostly used were copper, aluminum, and cadmium. We used the same "senders" which we and others employed in the biological yeast test methods. The results of our investigations with the physical detector methods may be stated briefly. The counts obtained with the photo-electric counter, when exposed to biological or chemical materials, did not fall outside the limits of fluctuation in the control of background counts. In experiments with yeast, as stated before, an apparent increase in growth rate was noted occasionally, but for a large series of observations fell within the range of variation in the control culture.

All in all, our experiments thus far failed to confirm the observations concerning the existence of mitogenetic radiation as reported by Gurwitsch and his co-workers. These negative results have also been obtained by a large number of other investigators. But we have not yet abandoned the study of the problem. We still feel that we might have worked with boundary methods which fall just short of the required sensitivity to detect mitogenetic radiation or that the Gurwitsch effect possibly represents a new phenomenon which does not easily lend itself to study with routine biological or physical testing methods.

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DESOXY-CORTICOSTERONE ACETATE IN ADDISON'S DISEASE WITH PRESENTATION OF A TYPICAL CASE

By Ed. J. Ryan, M.D. and E. Perry McCullagh, M.D.

Recent major advances in the management of adrenal cortical insufficiency include the use of cortical extracts[1,2,3], the use of added sodium chloride[4] and a low potassium diet[5]. Patients have been maintained in a reasonable degree of comfort with moderate activity for a number of years on such a program. The expense of the naturally derived cortical extract has been a matter of some concern, however.

Desoxy-corticosterone acetate*, produced by Steiger and Reichstein[6] and announced in 1937, is one of several synthetic adrenal cortical hormones, and is apparently identical with Kendall's substance B[7]. Reichstein and von Euw[8] have more recently demonstrated its presence in beef adrenals. Reports on its clinical application have been published by a number of investigators, including Levy-Simpson[9,10], Cleghorn et al[11], Thorn, Howard and Emerson[12], Wilkinson, Himsworth and Jones[10], Ferrebee, et al[13]. Chemically, it is closely related to progesterone[14].

We have treated six cases of Addison's disease with desoxy-corticosterone acetate for periods of six months to ten months. Dosage during various intervals of therapy has varied from 5 mgm. to as much as 20 mgm. daily. Added sodium chloride, 3 to 16 gm. per day as enteric-coated tablets, has been maintained in all cases, except during brief periods of observation. Potassium intake at first was limited in each case, but more recently severe dietary restrictions have been discontinued. Cortical extract in the form of eschatin** was given in four cases prior to initiating desoxy-corticosterone therapy.

Definite benefit was noted clinically in all cases. In two, complete symptomatic control resulted. In another two, the symptoms were materially lessened, but not completely alleviated, particularly the gastro-intestinal manifestations. In the remaining two, results were only moderately good, quite possibly a consequence of less consistent or inadequate treatment. At least 10 mgm. per day, in conjunction with other measures, was necessary before distinct initial improvement was obvious.

Blood pressure rise accompanied the use of desoxy-corticosterone in all six cases, and reached hypertensive levels in five. This has been observed particularly when 10 mgm. per day or more has been con-

*Desoxy-corticosterone acetate (Cortate) used in the treatment of these cases was supplied through the courtesy of Dr. I. Schwenk, Dr. Max Gilbert and the Schering Corporation.

**Eschatin is adrenal cortical extract produced by Parke, Davis and Co., and obtained for these studies through the courtesy of Dr. E. A. Sharpe.

tinued over a period of weeks or months, especially in conjunction with large doses of sodium chloride. The amount of clinical improvement has not paralleled the degree of hypertension. The mechanism by which the rise is brought about is not entirely clear.

Gain in body weight has likewise occurred as a result of desoxy-corticosterone therapy. In general, it may be said that the patients with the greatest weight gain showed the most striking degree of improvement.

Hemoconcentration has been corrected by the use of desoxy-corticosterone, although the amount of hemodilution has not necessarily been indicative of the degree of clinical response. The negative sodium and chloride balance of Addison's disease has likewise been converted to normal by the drug[15].

Low plasma sodium and chloride levels have tended to rise, and elevated plasma potassium has fallen with the administration of desoxy-corticosterone. These changes have not always been consistent with the clinical condition of the patient.

No alteration has been observed in temperature, pulse, pigmentation or glucose tolerance.

One case was treated by subcutaneous implantation of 400 mgm. of desoxy-corticosterone. According to Thorn[16], this should have permitted the absorption of about 2 mgm. of the substance daily. At the end of three weeks, during which time the sodium chloride intake was limited to 8 gm., and later to 3 gm. daily, she was extremely weak and drowsy, and no appreciable degree of clinical improvement could be detected. The addition of eschatin, 7.5 cc. twice a day, resulted in increased strength and almost complete abolition of muscular aching and gastro-intestinal symptoms.

Levy-Simpson and Himsworth[10] have suggested on clinical grounds that desoxy-corticosterone may not represent complete replacement therapy, an observation corroborated by our studies. In two cases, rather marked degrees of hypertension were maintained for several months without complete alleviation of symptoms. In one case, the drug was withdrawn for a month, at the end of which time the patient appeared on the verge of crisis, although the blood pressure, which had been low before treatment was begun, was still within the upper range of normal. Hemodilution has resulted without corresponding clinical improvement. In one instance, desoxy-corticosterone caused marked chloride retention without clinical changes, while the addition of eschatin did not affect the chloride balance but did produce marked clinical benefit.

Evidences of overdosage include the hypertension previously mentioned, and edema, which has been observed in two cases. One of these patients gained 14 pounds in six days, after receiving 175 mgm. of desoxy-corticosterone with added sodium chloride in nineteen days' time.

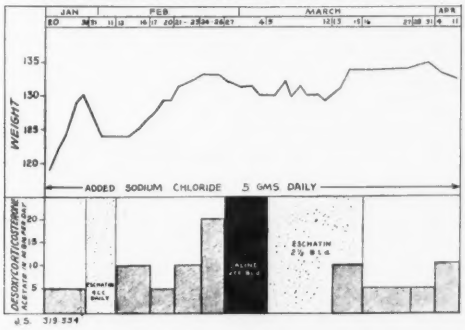
Another patient developed hydrops of each knee after receiving repeated injections of desoxy-corticosterone at the same site in each thigh a few inches above the knee.

The following case* is presented as illustrative of several of the features described.

The patient was a 38 year old man with symptoms highly suggestive of Addison's disease. Definite hyperpigmentation of the buccal mucosa was present. The sodium and chloride excretion test[18] *was typical of adrenal cortical deficiency. Injections of desoxy-corticosterone acetate, 5 mgm. per day, were begun on January 20, 1939. A low potassium diet and 5 gm. of added sodium chloride daily were used concurrently. Adrenal cortical extract in the form of eschatin was given in dosage of 5 cc. and 4 cc. daily for periods as shown on the charts.*

On this program, he gained 11 pounds in 11 days, and subsequent determinations of weight have varied with the dose of desoxy-corticosterone (chart 1).

THE EFFECT OF DESOXYCORTICOSTERONE ON WEIGHT

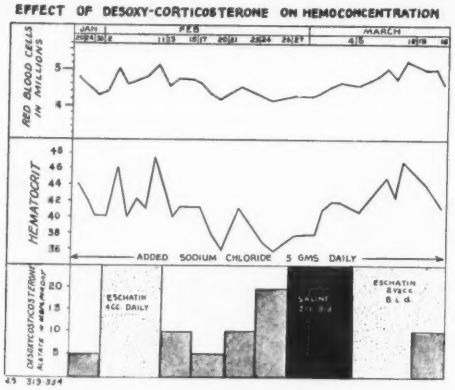


A similar parallel has been noted between hemodilution and desoxy-corticosterone dosage, as contrasted to the relative hemoconcentration when eschatin or saline alone were given (chart 2).

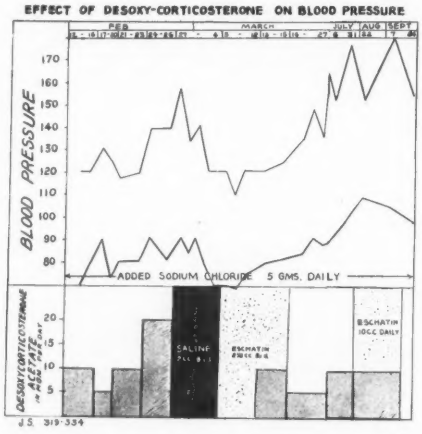
The dose of desoxy-corticosterone varied somewhat during his entire course of treatment. Five to ten mgm. per day were given from March 12 to May 5, up to which time improvement had been very meager. During the subsequent period, the diet was gradually liberalized, eschatin was not given, and the added sodium chloride was maintained at 5 gm. per day. For three weeks in May, doses of 15 mgm. to 20 mgm. daily were given. During this period, he showed definite improvement in strength, nervous stability and general sense of well-being. This degree of improvement continued on doses of 10 mgm. per day.

Arterial tension rose, varying with the dosage to some extent, but has been in hypertensive range on practically all occasions since June (chart

*This is the same as Case 3, previously reported[17].



3). It is of interest that he has not been entirely symptom-free in spite of this.



There was some trend of plasma sodium and chloride to higher levels during desoxy-corticosterone therapy. Plasma potassium levels are extremely variable (table I).

TABLE I.

	Sept. 4	*Jan 7*	*Jan. 24*	*Feb. 22*	*March 3*	*May 18*	*Aug. 18*	*Aug. 24*
Sodium	350	357	363	365	344	423	362	368
Potassium	18.9	22.9	16.9	16.7	19.2	19.7	15.5	18.7
Chloride	495	511	528	...	...	561	...	...

The addition to his program of eschatin, in doses of 10 cc. per day for fifteen days was accompanied by the disappearance of practically all re-

maining symptoms. Withdrawal of eschatin for a month, during which time the same dose of desoxy-corticosterone was continued, resulted in a recurrence of the muscular aching, mild fatigue and abdominal distress. Subsequently, the addition of eschatin again in the same dose for twenty-five days brought distinct clinical improvement.

From our observations we conclude that desoxy-corticosterone acetate is a valuable agent for the control of the symptoms of Addison's disease. It has a particularly powerful effect upon sodium, chloride and water balance. Overdosage effects may include arterial hypertension and massive edema of severe degree. For reasons mentioned, we believe it does not represent complete replacement therapy and should not be depended upon as the sole agent in therapy when symptoms are incompletely controlled by it or in the presence of crises.

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ANDROGENS IN THE MALE IN THE ABSENCE OF THE TESTES

D. Roy McCullagh, Ph.D. and Robert Daoust

That the testes are not the only source of androgenic material has long been recognized. Before laboratory methods of androgenic assay were available, many females with striking male characteristics were observed. The above characteristics in themselves constitute a qualitative assay for androgens and indicate their presence in these cases. Precocious sexual maturity has also frequently been reported in young males and excessive development of characteristics dependent on androgenic stimulation has been observed in adult males, in which there appeared to be reason to believe that the source of the androgens was extratesticular. A typical observation of this kind is exemplified in a case to be reported by Dr. V. C. Laughlin and Dr. E. P. McCullagh. This report will describe a boy four years of age with a penis anatomically and functionally that of an adult, a considerable growth of pubic hair, unusual prostatic growth, a low voice, and other signs of precocious sexual maturity but with testes only the size of a pea. The androgenic output in the urine was considerably greater than that expected from an adult. The clinical diagnosis is that of androgenital syndrome. The experiments described below throw further light on the subject of testes-adrenal relationship.

Another publication[1] gave a summarized account of some of the work reported herein. It was stated that androgens could be found in the blood of castrated rabbits. This in itself is not surprising, since comb-growth producing material has been demonstrated in the urine of several castrates. However, the detailed study of the experimental animals adds considerably to the understanding of the physiology of this phenomenon.

The rabbits employed in this work were all mature, healthy males. In examining their blood for androgens, the blood was removed from the heart by means of a hypodermic needle and syringe. In each case approximately 40 cc. of blood was withdrawn for examination. The amount varied somewhat because of technical difficulties and the condition of the animals. The differences, however, are not consequential.

The extraction of the androgenic material was accomplished as follows: The blood was made up to 400 cc. with distilled water and acidified with 20 cc. of concentrated sulfuric acid. On the assumption that part of the hormone was probably in an inactive form, as is the case in both urine and in testes, the mixture was hydrolyzed by boiling for 15 minutes. It was then extracted twice by stirring or by violent shaking for 15 minutes with 200 cc. of dibutyl ether. The extraction was some-

what complicated by emulsification which was controlled by the addition of sodium taurocholate. The combined dibutyl ether extracts were washed twice with 50 cc. of 10 per cent sodium hydroxide or saturated sodium bicarbonate and twice with 50 cc. of water, the sodium hydroxide and water being discarded. The ether was evaporated to dryness in vacuo. The residue containing the hormone was removed from the flask to a small beaker by dissolving it in diethyl ether; 5 cc. of sesame oil were added and the ether removed by evaporation on a water bath.

The assay of the androgenic material contained in the sesame oil was carried out by the procedure of McCullagh and Cuyler[2], in which the oil is administered by inunction on the combs of capons. In each case 5 capons were employed, each bird receiving 0.2 cc. of oil daily for five days. The increase in size of the comb expressed in millimeters (length plus height) is a measure of the amount of androgenic material present. The results in this paper are expressed as comb-growth and not as international units.

The effect of castration on the amount of androgen in the blood of rabbits is demonstrated in tables 1 to 4. Normally, the androgens from 40 cc. of blood caused a comb-growth of 3.7 mm. in each of 5 capons. A few days following removal of the testes the comb-growth is decreased to about 1.7 mm. However, after a month or more, the amount of androgen in the blood is normal and is still at the same level two and one-half years later. Although the amount of androgen (in this case meaning

TABLE 1

ANDROGENS IN BLOOD OF NORMAL MALE RABBITS

Animal Number	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
	cc.	mm.
1	40	4.2
2	39	2.4
4	40	3.6
4	37	5.8
9	42	6.4
11	36	3.0
11	39	2.0
13	37	3.4
14	35	3.0
12A	45	3.4
15	45	3.4
16	44	5.0
12B	45	3.6
	Average 40 cc.	3.8 mm.

TABLE 2

ANDROGENS IN BLOOD OF MALE RABBITS CASTRATED LESS THAN ONE MONTH

Animal Number	*Length of Time Castrated*	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
		cc.	mm.
11	25 days	40	2.0
13	20 days	36	1.8
12	20 days	38	1.6
14	3 days	42	1.4
		Average 39 cc.	1.7 mm.

TABLE 3

ANDROGENS IN BLOOD OF MALE RABBITS CASTRATED FOR ONE OR MORE MONTHS

Animal Number	*Length of Time Castrated*	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
		cc.	mm.
4	4 weeks	40	4.8
9	4 weeks	38	1.8
9	4.9 months	45	5.4
4	4.9 months	45	3.0
14	3.5 months	45	5.0
		Average 44 cc.	4.0 mm.

TABLE 4

ANDROGENS IN BLOOD OF MALE RABBITS CASTRATED 2½ YEARS

Animal Number	*Volume of Blood Extracted*	*Average Comb-growth in 5 Capons*
	cc.	mm.
3	40	5.0
10	35	5.6
5	38	2.0
6	36	2.4
7	37	4.0
8	37	3.8
5	45	5.0
6	45	2.8
8	45	3.0
	Average 40 cc.	3.7 mm.

comb-growth producing material) in the blood of castrated rabbits becomes normal, the animals are by no means androgenically normal. That is to say, the changes usually associated with lack of testicular androgen remain quite evident after the blood androgens become normal. The weight of the pituitary gland increased from an average of 24 mg. to 34 mg. The prostate decreased from 570 mg. to 185 mg. and the seminal vesicles showed similar atrophy. The adrenals increased in weight from 340 to 864 mg.

Discussion

Although final proof is not as yet complete, it would seem very probable that the androgens found in the blood of castrated rabbits originate in the adrenal glands. It is well known that the adrenals contain androgenic tissue. This subject is reviewed by Grollman[3]. Although at one time it was thought that only man and mouse had androgenic tissue in the adrenals, it is now known that rabbit, rat, cat, and monkey also possess it. This makes it seem probable that it is common to most mammals. There is also evidence to indicate that an homologous tissue is to be found in birds. The androgenic tissue which is frequently referred to as the X-zone of the adrenals normally exists only during early life. It is the same morphologically as the accessory adrenals which are sometimes situated some distance from the main glands and which usually disappear at an early age.

The X-zone is embryologically and morphologically quite distinct from the rest of the adrenal glands, and there is no reason to believe that it is physiologically related to either the medulla or the cortex. Since the X-zone disappears normally early in life, its only function would seem to be confined to the fetal and infantile period of an animal's existence. At that time it is physiologically active, and according to Burrill and Greene[4], in the absence of the gonads in the immature male rat, the adrenals are responsible for the maintenance of the ventral prostate gland in a normal or nearly normal condition. These, however, demonstrate that the adrenals are not appreciably involved in the normal development of the prostate.

From a chemical point of view, adrenal products are closely related to the sex hormones. Several substances have been isolated from the adrenal gland which are closely related to the sex hormones, in that both the adrenal substances and the sex hormone are derivatives of cyclopentanoperhydrophenanthrene. At least one of these adrenal compounds, namely adrenosterone, has been shown by Reichstein to possess androgenic activity. Similarly, progesterone is androgenically active, and has been isolated from adrenal tissue.

The blood androgens were apparently normal but the secondary sex glands of the castrated rabbits showed no signs of the existence of any

androgens. This indicates either that the androgen in the blood of castrated rabbits is not in an active form and is activated during the process of extraction or that it is an androgen to which the capon's comb responds more readily than do the secondary sex glands of the rabbit, in that way differing from the testicular androgen.

Hall and Korenchevsky[5] have studied the changes in the rat adrenal following castration and have shown that several different androgens will correct those changes. Unfortunately, by present methods, it is not possible to determine whether the adrenal androgen output and hence blood androgen is normal when androgens are being injected into castrated animals. It would be interesting, however, to investigate the effect of non-androgenic steroids on the adrenals of castrated animals.

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MYXEDEMA HEART

WILBUR E. FLANNERY, M.D. and A. CARLTON ERNSTENE, M.D.

The term "myxedema heart" was first employed by Zondek[1] in 1918 to describe a syndrome due to myxedema and consisting of enlargement of the heart, sluggish cardiac movements, electrocardiographic changes, and congestive myocardial failure. Although Zondek's observations have been fully confirmed, it has been well established also that myxedema only rarely is complicated by congestive heart failure. Enlargement of the heart and changes in the electrocardiogram occur commonly, however, and the term myxedema heart has now come to be applied to these changes even though evidence of congestive failure is absent. Organic heart disease may also be present, and because of this, the cardiac abnormalities in any case of myxedema must be shown to be amenable to therapy with thyroid substance before one can conclude that they were due to myxedema heart.

The present report is based on eight cases of myxedema in which electrocardiograms were made at the time the condition was first diagnosed (table 1). In two of the cases the symptoms had developed three months and nine years, respectively, after thyroidectomy, while in the other six, the condition was of spontaneous origin. The age of the patients ranged from 37 years to 68 years. Five were women and three were men. The initial basal metabolic rates ranged between —24 per cent and —41 per cent, and the plasma cholesterol concentrations between 196 mgm. per 100 cc. and 248 mgm. per 100 cc. The resting pulse rate ranged from 48 to 78 beats per minute, the systolic blood pressure from 108 to 160 mm. of mercury, and the diastolic pressure from 70 to 100 mm. of mercury.

Roentgenograms of the chest were made in five cases before the institution of treatment, but in only two of these were additional films made at a later date. In four of the five cases the transverse diameter of the heart shadow exceeded one-half the internal diameter of the chest by 0.6 cm. to 1.5 cm. In the other case, cardiac enlargement appears to have been present also for the transverse diameter of the heart shadow after four months of treatment with thyroid substance was 1.8 cm. less than in the original films.

Electrocardiographic abnormalities were recorded in all eight cases (table 1). The P-waves were iso-electric or of subnormal amplitude in all. The QRS complexes were of low voltage in four, while in a fifth, although the voltage was within normal limits at the beginning of treatment, thyroid therapy resulted in an increase in amplitude. In all eight cases, the T-waves were of low amplitude, iso-electric, or inverted in all three conventional leads. T-IVF was inverted in three of the five cases in which precordial leads were recorded. Auriculoventricular conduc-

TABLE 1
THE HEART IN MYXEDEMA

Case No.	*Age Years*	*Sex*		*Basal Metabolic Rate Per Cent*	*Plasma Cholesterol mgm/100cc.*	*Pulse Rate*	*Electrocardiogram*	*Internal Diameter of Thorax cm.*	*Transverse Diameter of Heart cm.*	*Blood Pressure*	
										Systolic mm. Hg.	*Diastolic mm. Hg.*
1	56	F	Before treatment	−36	263	58	P-waves iso-electric. Low voltage of QRS. T-I and II inverted. Low T-III. T-IV F inverted.	30.0	16.5	150	98
			4 weeks after beginning treatment	−4	128	62	P-I iso-electric. P-II and III normal. QRS complexes of greater amplitude. T-I, II, and IV F upright. Low T-III.	30.0	14.0	132	84
			6 months after beginning treatment	−5	183	60	P-I, II, and III upright. QRS complexes of greater amplitude. T-I, II, III, and IV F of greater amplitude.	30.4	16.5	128	86
2	60	F	Before treatment	−24		72	Low P-waves. Low voltage of QRS. T-I, II, III, and IV F inverted. Left axis deviation.	28.0	15.2	160	98
			One month after beginning treatment	±0		82	P-waves and QRS complexes of greater voltage. T-I, II, and IV F upright. T-III inverted. Left axis deviation.	29.2	15.2	130	98
3	68	F	Before treatment	−38	333	78	Low P-waves. P-R = 0.24 second. QRS complexes of normal amplitude. T-I, II, and IV F inverted. T-III diphasic. Left axis deviation.			110	90
4	57	F	Before treatment	−28	348	93	Low P-waves. QRS complexes of normal amplitude. Low T-I. T-II, III inverted. T-IV F normal.	29.2	15.2	130	98
5	45	M	Before treatment	−31	277	48	Low P-waves. QRS complexes of normal amplitude. Low T-I. T-II iso-electric. T-III inverted. T-IV F normal.			110	90
6	37	M	Before treatment	−41	196	104	Low P-waves. QRS complexes of normal amplitude. Low T-I. T-II and III inverted.	31.8	14.5	138	100
			4 months after beginning treatment	−17	136	104	Normal P-waves. QRS complexes of greater voltage. T-I normal. T-II upright but low. T-III inverted.	31.8	12.7		
7	43	F	Before treatment	−38	333	66	Low P-waves. QRS complexes of low voltage. Low T-I. Flat T-II. Inverted T-III.			125	70
			4 months after beginning treatment	±	200	78	P-waves and QRS complexes of normal amplitude. T-I and II normal. T-III inverted.				
8	38	M	Before treatment	−40	300	65	P-waves and QRS complexes of low voltage. T-I inverted. Low T-I and II.			108	86

tion was prolonged in one case but it is not certain that this change was due to myxedema, since no subsequent tracings were made after the patient had been receiving thyroid substance. In four cases additional electrocardiograms were made after the patient had been receiving thyroid substance for one to five months, and in all, the original abnormalities were found to have been corrected.

None of the eight patients presented signs of congestive heart failure, but five had experienced dyspnea on slight or moderate exertion.

The following case report illustrates the most important features of myxedema heart not accompanied by congestive heart failure.

Case Report

Case 1: A white married woman, 56 years of age, had experienced an attack of influenza two years before and shortly afterward noted swelling of the soft tissues of the head and face and puffiness under the eyes. The swelling varied in degree from day to day and was usually worse in the mornings. After one year, swelling, burning pain, and paresthesia had developed in the hands, and to a lesser degree in the feet. The sensory disturbances were aggravated by exposure to cold. The hair had become drier and the skin dry and rough. The weight had increased, but the actual amount gained was not known. Weakness, fatiguability, and apathy were prominent symptoms, and there was mild dyspnea on limited exertion.

Physical examination: The patient was 61½ inches tall and weighed 174 pounds. The face was full and the expression dull. There was distinct puffiness about the eyes. The hair was thin and dry and the skin dry and of a lemon-yellow tint. The tongue was full and thick. There was no palpable thyroid tissue. The lungs were clear on percussion and auscultation. The area of relative cardiac dullness extended 11 cm. to the left of the midsternal line in the fifth intercostal space. The heart rhythm was regular and the rate 52 beats per minute. A faint systolic murmur was present over the aortic area. All heart sounds were of average quality. The peripheral arteries were not appreciably thickened, and the arterial pressure was 150 mm. systolic and 98 mm. diastolic. The liver was not enlarged or tender. The hands, forearms, feet, and lower legs appeared swollen but there was no pitting edema.

Examination of the urine gave normal findings. The red blood cell count was 4,130,000 per cu. mm., and the hemoglobin content 71 per cent. The white blood cell count was 6,150 per cu. mm. The plasma cholesterol content was 263 mgm. per 100 cc., and the Wassermann and Kahn reactions of the blood were negative.

The basal metabolic rate was —36 per cent. A teleroentgenogram showed the transverse diameter of the heart shadow to be 16.5 cm. and

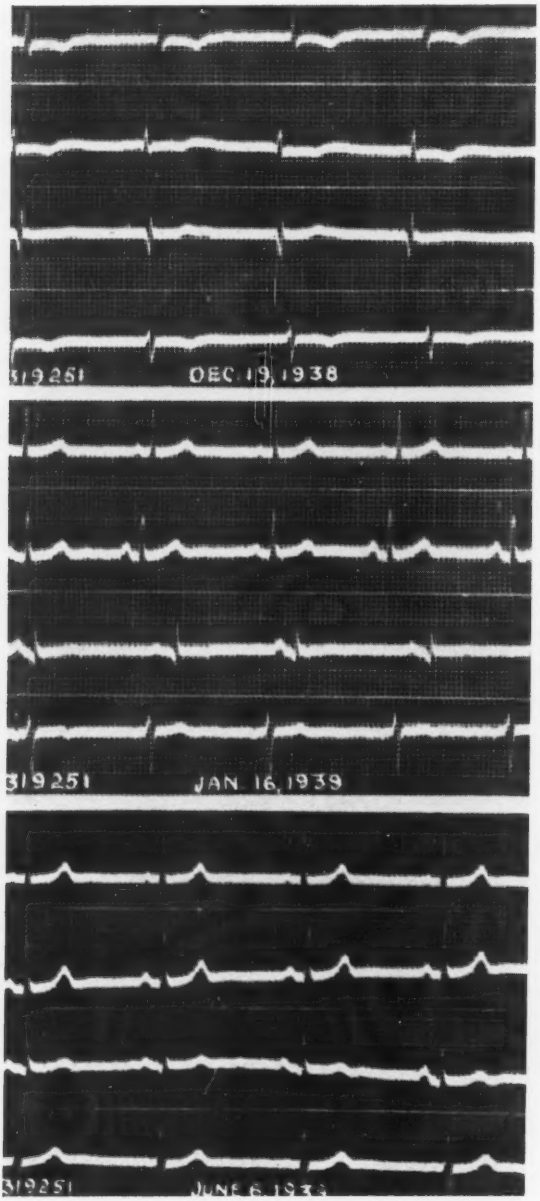

FIGURE 1: Electrocardiograms of patient discussed in Case 1.

the internal diameter of the thorax 30 cm. An electrocardiogram (figure 1) showed sinus rhythm with a rate of 58 per minute. The QRS complexes were of low voltage and the P-waves were iso-electric in all leads. The T-waves were inverted in leads I, II, and IV F and of low amplitude in lead III.

Armour's desiccated thyroid was prescribed in doses of three grains daily for two weeks, and the dosage was then reduced to two grains daily. Twenty-seven days after beginning treatment, the patient's weight had decreased to 151 pounds and there was striking improvement in her general appearance. The basal metabolic rate was —4 per cent and the plasma cholesterol content 128 mgm. per 100 cc. The electrocardiogram (figure 1) was normal except for an iso-electric P-I and a flat T-III. The heart rate was 60 beats per minute. The patient was advised to continue to take two grains of desiccated thyroid daily for one more month, and then to reduce the dose to one grain daily.

Six months after the institution of therapy, the patient's general appearance was quite normal and she complained only of occasional tingling in the hands. The weight was 129 pounds, the pulse rate 60 beats per minute, and the blood pressure 132 mm. systolic and 84 mm. diastolic. The basal metabolic rate was —5 per cent and the plasma cholesterol content 183 mgm. per 100 cc. A teleroentgenogram showed the transverse diameter of the heart shadow to be 2.5 cm. smaller than at the time of the first examination. The electrocardiogram was within normal limits except for a low P-I (figure 1). The red blood cell count was 4,470,000 per cu. mm. and the hemoglobin content 84 per cent. The patient was advised to continue to take one grain of desiccated thyroid daily.

Discussion

Knowledge of the pathology of myxedema heart is based on the examination of only a small amount of material[2]. The significant changes consist of interstitial edema and more or less myocardial fibrosis. Coronary artery sclerosis is often present. The increase in the size of the cardiac shadow in teleroentgenograms has been variously explained in the past as the result principally of hypertrophy of the heart, dilatation of the heart, or pericardial effusion. The prompt and often considerable diminution in the size of the shadow after the institution of treatment with thyroid substance is strong evidence against the presence of any great degree of true hypertrophy. Pericardial effusion is present at times, but in most cases of myxedema neither the clinical findings nor the roentgenographic appearance are consistent with the presence of significant amounts of fluid in the pericardium[3]. There is general agreement at present that the cardiac enlargement in myxedema is due chiefly to dilatation, but interstitial edema may be a minor contributory factor.

Changes in the electrocardiogram occur even more commonly in myxedema than does enlargement of the heart. Although many types of abnormalities have been recorded, the only one that is characteristic consists of iso-electric or inverted P- and T-waves in all leads. The QRS complexes, however, are often of subnormal amplitude.

Neither the electrocardiographic abnormalities nor the cardiac enlargement of myxedema are corrected by the use of digitalis. Thyroid substance in adequate amounts, on the other hand, brings about a complete return of all changes to normal. Overdosage must be carefully avoided, and whenever the heart is considerably enlarged or there is a history of angina pectoris, only small amounts of thyroid should be given. The effect of treatment on the basal metabolic rate, heart size, and electrocardiogram should be checked periodically, and as soon as the maximum degree of improvement has been attained, the daily dose of thyroid should be reduced to the lowest level that will maintain this state.

Summary

The roentgenographic and electrocardiographic findings in eight cases of myxedema heart have been summarized, and one case has been reported in detail.

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STAPHYLOCOCCUS SEPTICEMIA WITH SEPTIC ARTHRITIS OF THE KNEE TREATED WITH SULFAPYRIDINE

Report of a Case

J. I. KENDRICK, M. D.

The following case is reported because of the very favorable result obtained from the oral use of sulfapyridine and multiple aspirations and irrigations of a septic joint.

REPORT OF A CASE

A boy, 14 years of age, came to the Clinic on May 3, 1939, complaining of pain in the left knee which had begun 5 days previously. The patient was an active boy. Shortly before the onset of the pain there had been definite trauma to the knee in the form of a bruise. This had not been sufficient to disable him. Following the injury an acute febrile reaction occurred and pain developed in the left knee. Treatment prior to admission to the hospital had been palliative.

The family and personal histories revealed nothing of importance. He had had the usual childhood diseases but no serious illnesses. During the past year he had had recurrent attacks of tonsillitis.

Physical examination showed a patient obviously acutely ill. The temperature was 103° F., the pulse rate 122 per minute, and the respirations 20. The tonsils were moderately enlarged, cryptic, and injected. Examination of the chest, heart, and abdomen revealed no abnormal findings. The left knee was maintained in a position of flexion and any slight movement caused excruciating pain. There was very definite evidence of peri-articular thickening and acute tenderness was present over the medial aspect of the joint adjacent to the joint line. The synovial reaction was marked as shown by an increase in the joint fluid and distention of the quadriceps pouch.

Roentgen examination of the bones showed no pathological change. There was rather marked widening of the joint space due to the distention of the joint with fluid.

Laboratory Findings: Examination of the blood showed 3,770,000 red cells with 68 per cent hemoglobin. There were 8,050 white cells with a differential count of 67 per cent polymorphonuclear cells, 28 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophils. The urine was normal.

A clinical diagnosis of septic arthritis of the left knee was made.

The patient entered the hospital on May 3, 1939. On the following day the knee was aspirated and 70 cc. of thick, greenish, purulent fluid

was withdrawn. Microscopic examination of the fluid revealed many white blood cells but the culture was negative. A blood culture taken on the day of admission was positive for staphylococcus aureus. On May 7th, the knee was again aspirated and 70 cc. of thick, flocculent fluid withdrawn. Culture of the fluid on this occasion was positive for staphylococcus aureus.

The immediate treatment consisted of general supportive measures and extension of the leg. A transfusion of 500 cc. of whole blood was given. During the first 5 days in the hospital sulfanilamide was administered but the septic temperature continued. On the fifth day sulfanilamide was discontinued and sulfapyridine started. The knee became so distended it was necessary to aspirate the joint at intervals of two to three days. Following aspiration, the joint was irrigated with 500 to 1000 cc. of normal saline solution. After starting sulfapyridine, the septic temperature gradually subsided. Five days later the temperature was normal and continued so throughout the rest of the stay in the hospital. While in the hospital the knee was aspirated and irrigated eight times.

The patient left the hospital on the twenty-eighth day (May 31, 1939). There was full range of motion without pain in the knee. The only significant physical finding was a slight increase of fluid in the joint.

Following discharge from the hospital, activity was limited for 7 weeks. An examination on July 22, 1939, revealed full range of motion in the joint and no evidence of peri-articular change or areas of tenderness. The roentgen examination of the knee at that time showed no abnormal bone or joint change. Following this observation more activity was permitted.

He was again observed on August 3, 1939, at which time there were no findings of significance. Normal activity was allowed.

Summary

This case has been reported because of the importance of early diagnosis and treatment of septic arthritis of a joint and also because of the very favorable result obtained from the oral use of sulfapyridine and multiple aspirations and irrigations. It is difficult to evaluate the exact role which the sulfapyridine had in the treatment but, because of the prompt fall in temperature following administration of this drug, it was probably of definite benefit. It is doubtful if any other method of treatment could have effected a more favorable result.

ANEURYSM OF THE INNOMINATE ARTERY

Report of a Case

GEORGE CRILE, JR., M.D., AND H. F. ELIAS, M.D.

Aneurysm of the innominate artery is not common and comprises only about 3 per cent of all aneurysms. This type of aneurysm is of special interest to the surgeon as its diagnosis is not as hopeless as that of the aortic aneurysm for which it may be mistaken. The treatment is within the province of surgery as has been demonstrated by Rundle[1], who collected seven cases successfully treated by excision of the innominate artery, and by Schwyzer[2], whose case was living and well 22 years after operation. Early diagnosis and treatment are desirable as adherence to the sternum, vascular complications, (especially cerebral), and the accumulation of large amounts of clot in the aneurysmal sac are all said to decrease the likelihood of obtaining a good result from surgery.

The innominate artery is the first branch of the arch of the aorta, and is usually 4 to 5 cm. long. It most frequently arises at the level of the upper border of the second right costal cartilage, ascending obliquely upward, backward and to the right. At the level of the upper border of the right sternoclavicular articulation it divides, forming the right common carotid and right subclavian arteries. Excision or ligation of this artery can be successfully accomplished if adequate collateral circulation has been established.

The following is the report of a case of a large innominate aneurysm.

A 52 year old colored coal miner entered the Clinic on July 24, 1939, complaining of a lump in his neck and right chest of 18 months' duration. The mass was first noted as a painless swelling, and was not related to any known trauma. There had been progressive increase in size of the mass with associated local pain and dull ache in the right arm present for the past 7 months. In the past 2 months, the patient had noted a change in his voice and a choking sensation when in the recumbent position. There had been no nocturnal or exertional dyspnea, but a nonproductive cough had been present for some time.

Family history: Noncontributory.

Marital history: Married—wife living and well. Two children died in infancy and the last pregnancy was a miscarriage.

Past history: Past illnesses included mumps, tonsillitis and influenza in 1918. Patient denied venereal disease by name and symptoms.

Physical examination revealed a colored man, 65 inches tall, weighing 123 pounds, temperature 98.2°, pulse 96, blood pressure, right arm 134/104, left arm 122/100. The skin was dry and the mucous membranes were normal. The pupils were equal and reacted slowly to light. The teeth were carious and there was considerable pyorrhea alveolaris.

FIGURE 1: Photograph showing anterior view of innominate aneurysm.

Both vocal cords were thickened but of normal color. The left cord did not approximate well in the midline but motion of both cords was demonstrated. Examination of the neck revealed a mass extending from the level of the hyoid bone down to the third intercostal space. The mass was 8 inches wide and protruded approximately 6 inches from the anterior chest wall (figs. 1 and 2).

The mass pulsated forcefully with the heart beat. On the right anterolateral surface of this mass, over an area 3 inches in diameter, the skin was crusted and was obviously breaking down. The superficial vessels

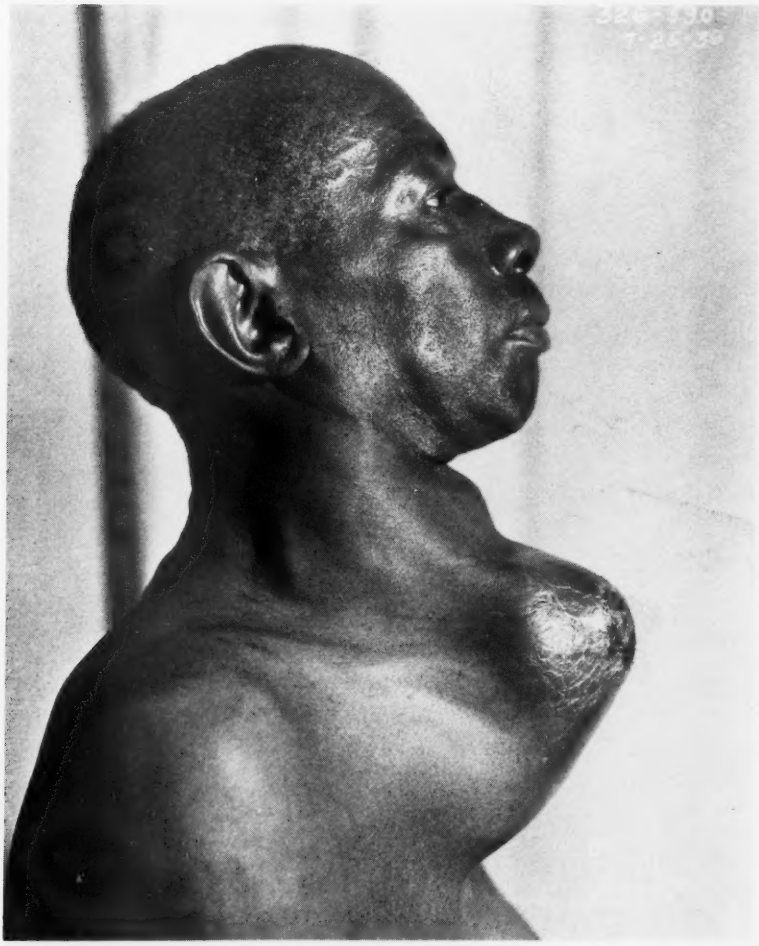

FIGURE 2: Photograph showing lateral view of aneurysm with crusted area.

in the right cervical region were dilated. Both carotids could be palpated pulsating synchronously behind the main body of the tumor. All vessels were thickened and sclerotic.

The lungs were clear to percussion and auscultation. The cardiac borders were not enlarged, the heart sounds were rhythmic, of good quality and no murmurs could be heard. The radial pulses were equal and synchronous. The remainder of the examination, including neurological examination, showed no abnormalities. There were no penile scars.

Laboratory examination revealed the following data:

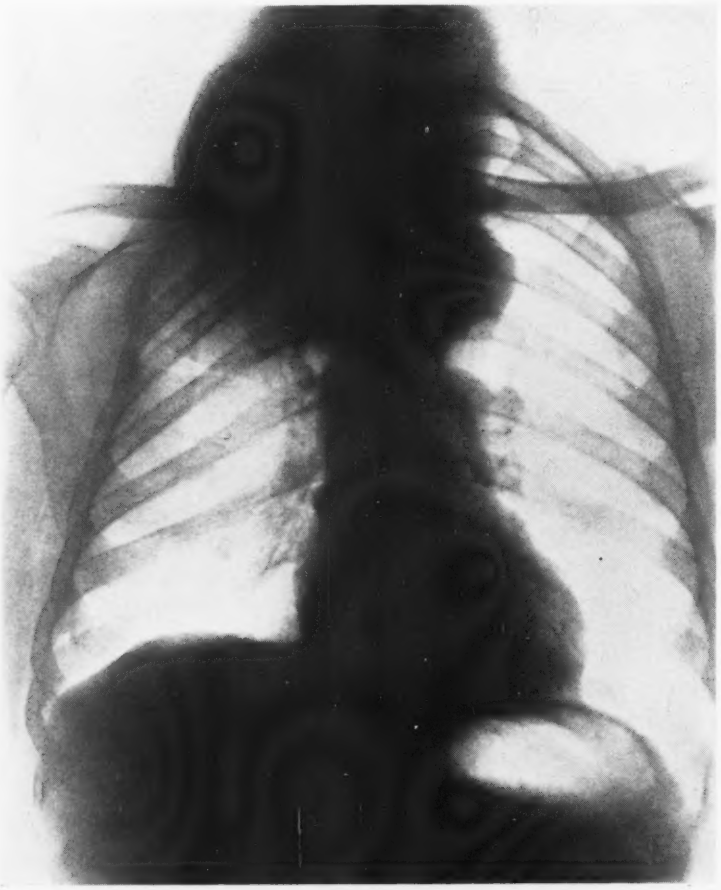

FIGURE 3: Roentgenogram showing mass pushing clavicles anteriorly and lateralward. The sternum is not eroded.

Blood: Red blood cells 3,740,000, hemoglobin 50 per cent, white blood cells, 4,900; neutrophils 78; eosinophil, 1; lymphocytes, 21. Blood sugar fasting was 92 mgm. Wassermann and Kahn tests were negative. Recheck of Wassermann and Kahn tests again gave negative reactions.

Urinalysis was negative.

Roentgenograms of the chest showed the mass as seen in figure 3.

The shadow of the aorta was interpreted as showing no abnormalities.

An electrocardiogram showed no diagnostic changes.

The basal metabolic rate was +11 per cent.

To differentiate between a pulsating thyroid neoplasm and an

aneurysm of the innominate artery, a 24 gauge needle was inserted at the periphery of the mass and bright red blood under high pressure was obtained.

Because of the enormous size of the aneurysm, it was questionable if any operative procedure could be undertaken, especially in view of the fact that rupture of the mass was thought to be near at hand, and would surely take place if any incision was made in the adjacent skin. We felt, however, that if exposure were possible, an endaneurysmorraphy with repair of the defect in the vessel might be accomplished. The next day, while plans were being made for operation, the aneurysm spontaneously ruptured during an attack of coughing. The rupture would admit a pencil tip but fortunately was closed quickly by application of pressure. Bleeding was controlled temporarily by pressure and the patient was taken to the operating room.

A cannula was introduced into the femoral vein and was connected with a large container of normal saline. Pressure was removed from the aneurysm and the blood spurting from the aneurysm was collected in a container and citrated, three liters of blood being obtained. This was transferred to the vessel of normal saline connected to the femoral vein. The patient became unconscious as the third liter was obtained and the blood flow diminished. The aneurysm was immediately incised widely, the blood was collected, the clots were removed and the opening was found. The opening was only about 2 cm. in diameter and appeared to be located at the junction of the subclavian and innominate arteries, involving the anterior wall of the vessel. The opening was rapidly closed with three layers of continuous steel alloy sutures and the blood and saline were simultaneously injected in the femoral vein. Artificial respiration was started and adrenalin was injected into the femoral vein. The apex impulse was visible but no heart sounds could be heard. After a five minute interval, during which time artificial respiration was maintained and intracardiac adrenalin had been administered, a hockey stick incision was made over the sternum, the ribs of the precordium were reflected and the heart was massaged. No response was obtained. Exploration revealed a large post-mortem blood clot filling the aorta. The medial third of the right clavicle had been completely destroyed by the aneurysm.

Comment

This unusually large aneurysm of the subclavian artery was obviously not well suited to surgical treatment as the size greatly increased the technical difficulties and the thin wall of the sac made any manipulation about the area hazardous.

In view of the size of the aneurysm, the age of the patient and the degree of arteriosclerosis present, it was believed that ligation of the innominate artery could not be successfully accomplished. It was there-

fore decided to attempt to repair the aneurysm by endaneurysmorraphy. The size of the tumor and the thinness of its walls precluded the possibility of exposing the innominate artery and temporarily controlling its circulation while the aneurysm was being repaired.

Before the aneurysm ruptured and forced us to play our hand before we were prepared, we had planned the operation in the following steps:

1. Slow exsanguination of the patient, removing a pint of blood every six hours until the hemoglobin reached dangerously low levels.
2. Storing of all blood removed.
3. Procuring an additional 1000 cc. of blood from matched donors.
4. Insertion of large cannulas in both femoral veins and in the arm veins and connecting these cannulas with reservoirs containing the blood and adrenalin.
5. Wide incision of the aneurysm with collection of the blood and transfer of blood to the previously prepared reservoirs.
6. After "death" by rapid exsanguination, rapid endaneurysmorraphy was to have been performed. (It was estimated that the first layer of sutures could be inserted in one or two minutes.)
7. Rapid autotransfusion of blood and adrenalin and an attempt to resuscitate the patient while repair of the aneurysm was being completed.

Unfortunately, when the aneurysm ruptured we had not as yet procured the necessary cannulas and furthermore the patient was already in mild shock from loss of blood. No blood was immediately available for transfusion. We had therefore to rely on glucose solution to replace the blood lost in hemorrhage.

Collection of the blood from the aneurysm was easily accomplished and the sac was found as we had expected, to have a small mouth and to be well adapted to repair. Only about one and one-half minutes elapsed between the collapse of the patient and the completion of the first row of sutures in the repair of the aneurysm.

However, the femoral cannulas were not large enough and the blood was not delivered with sufficient rapidity. Nearly seven minutes had elapsed between the patient's collapse and the transfusion of enough fluid to replace the amount lost. In spite of the fact that the heart beat faintly for a few moments after the administration of intracardiac adrenalin, it was apparently too late for resuscitation to be effective.

This case has proved to our satisfaction that such an attack is feasible from the technical standpoint provided that with adequate preparation, rapid delivery of the blood could have been effected. Post-mortem examination of the repaired aneurysm showed the defect in the vessel wall well closed and the lumen of the vessel patent.

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CLINICAL ASPECTS OF THE ENDOCRINE FUNCTIONS OF THE TESTES IN MAN*

WILLIAM E. LOWER, M.D.

That the principal and accessory sex organs as well as many secondary sex characteristics of male animals are dependent upon the endocrine function of the testes has been conclusively shown by experiments in many research laboratories. Recent scientific clinical observations in human castrates have attested to the same fact. The spermatogenic elements of the testes may be destroyed by roentgen irradiation or by cryptorchidism without alteration in the sexual characteristics. It is believed that the interstitial cells of the testes produce one or more substances which act as pituitary depressants and sex stimulants. Such substances, whether natural or synthetic, are collectively known as androgens. The clinical problems which must be considered in the light of these findings have been approached from several different angles by various workers. At the Cleveland Clinic we have attempted to obtain as complete and consolidated a picture of testicular physiology and physiopathology as possible. We have therefore attacked the problem from several points, some of which are discussed in this paper. Particular attention has been directed to bio-assays and their results, the problem of prostatic hypertrophy, the question of the diagnosis and treatment of hypogonadism, the endocrinological aspects of spermatogenesis, and the results of experiments with testicular transplants.

BIO-ASSAYS IN THE STUDY OF TESTICULAR DISORDERS

In recent years it has become increasingly obvious that the clinical diagnosis of endocrine disorders can sometimes be considerably facilitated by a proper study of the hormone content of the body fluids. By proper methods of assay it is sometimes possible to determine the state of activity of an endocrine organ when all other known procedures are inadequate. This is particularly true in disorders of the pituitary gland and of the gonads. A review of the many papers on this subject is impossible here, but a summary of the methods now employed for clinical studies at the Cleveland Clinic is included.

THE EXTRACTION AND ASSAY OF ANDROGENS FROM BLOOD AND URINE

The methods employed were devised and described by McCullagh and McLin[1] and McCullagh and Osborn[2]. When working with blood it is diluted with 10 volumes of water and treated in the same fashion as urine. The urine or blood is hydrolyzed by boiling for 15 minutes with 5 per cent sulphuric acid and extracted twice with dibutyl ether. The ether is washed with alkali and water and evaporated to dryness by steam

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distillation in partial vacuum. The residue contains the hormone and is dissolved in sesame oil.

The quantity of hormone in the sesame oil is assayed by a modification of the method of Gallagher and Koch[3]. The details of the procedure for assay have been published by McCullagh and Cuyler[4].

The principle of the Gallagher and Koch method is that of producing growth in the comb of a capon. Several capons must be used for each assay. In dealing with moderate amounts of hormone, (e.g. the amount found in a 24 hour specimen of urine) the sample being tested can be injected into the pectoral muscles of the birds. When working with smaller quantities of hormone the test can be made about 35 times more sensitive by inuncting the hormone into the combs of the birds instead of injecting it into their muscles. The inunction method must be used for the quantitative measurement of the amount of androgenic material in blood.

The excretion of urinary androgens has received extensive consideration here[5] and in several other laboratories[6]. In normal men, approximately 20 to 80 international units are excreted daily. If testosterone propionate is injected into normal individuals, there ensues a prompt increase in the excretion of androgenic material. This is followed by a period of subnormal androgenic excretion and then a return to normal. The period of subnormal excretion probably represents a period of pituitary depression caused by the injection of the testosterone propionate. When testosterone propionate is injected into hypogonadal individuals, the urinary androgens increase in proportion to the dose. Following a single moderate dose the increased excretion lasts for only about 24 hours; larger doses effect an increase for several days.

The gonadotropic hormone: It is well known that the pituitary gland and the testes are closely interrelated. In the absence of pituitary hormone the testes produce no hormone, and except when proper hormonal therapy is instituted the spermatogenic function of the testes disappears following ablation or removal of the pituitary. Following castration there is an increase in activity of the pituitary gland. The histological picture changes, the gland increases in size, and an increased amount of gonad-stimulating hormone appears. Therefore, in studying prostate-pituitary-testes interrelationship it has seemed advisable to make quantitative measurements of the amount of pituitary gonadotropic hormone appearing in the urine. These studies have been made by a modification of the method of Heller[7].

The method consists essentially of removing certain toxic substances from the urine with 50 per cent alcohol and then precipitating the hormone by increasing the alcoholic concentration to 80 per cent. The amount of hormone present is ascertained by injecting it into immature

female rats and measuring the extent of the stimulation of the ovaries and uteri.

Normal young men excrete only traces of this hormone. Patients suffering from hypogonadism of testicular origin excrete large quantities. In numerous elderly men with decreased testicular function, large quantities of the pituitary gonadotropic hormone have been found. This has been observed in several individuals with prostatic hypertrophy. It is not, however, by any means indicative of that disease only.

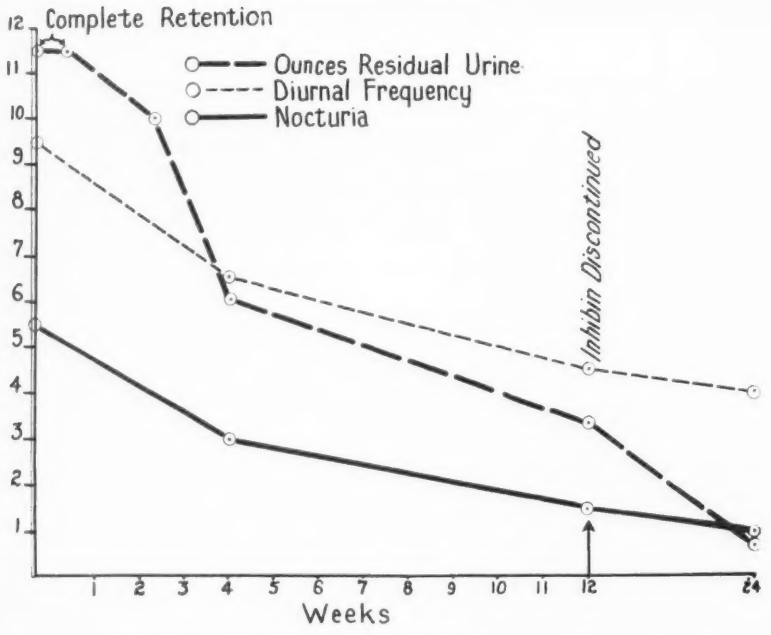
Prostatic Hypertrophy

A general discussion of the question of obstruction of the neck of the bladder is beyond the scope of this paper. One aspect of this problem, however, must receive our consideration. It has been my contention[8] that certain types of prostatic enlargement are the results of an endocrine disorder involving the testes and pituitary gland. For reasons which have received extensive consideration in earlier publications, we thought it probable that some hormone other than testosterone might be elaborated in the testes. The possibility that a deficiency of this second hormone which was tentatively termed "inhibin" could be a factor in the production of prostatic changes led to the administration to patients of a desiccated preparation made from whole bovine testes. We have now had the opportunity of observing the results of this therapy over a number of years. The hormone has been prescribed largely for patients having the clinical picture of benign enlargement of the prostate, that is, the large, soft, boggy glands. We asked a number of colleagues in other cities to cooperate with us in treatment along these lines and a certain number of them reported that in some cases they seemed to get rather striking results, characterized by relief from symptoms and urinary retention, with less residual urine, nocturia and diurnal frequency, usually less hesitancy and increased force of the urinary stream. McComb and Pearse[9] reported results by this method of treatment. It is obvious that as we have not fractionated the product and obtained the active principle, general application is not practical.

We appreciate that, following catheterization, a group of patients with urinary retention due to prostatic hypertrophy will improve and be relieved temporarily but, in our experience, no such percentage as shown here obtained the same amount of relief as the patients treated with the testicular preparation.

Chart I shows some of the results obtained in most of the cases that were benefited by the treatment.

Use of this non-surgical approach to the treatment of prostatic hypertrophy involved the usual difficulties encountered in endocrine replacement therapy. Even in those cases where there was a favorable reaction,



continued medication was required to prevent probable relapse. In some cases, even though the immediate effect of administration of hormone was most salutary, continued treatment failed to maintain satisfactory urinary function.

The failure of this type of treatment in a large percentage of cases is probably due to numerous causes. In a few cases in which we did not see improvement the condition may have been other than prostatic hypertrophy of endocrinological origin. In some instances it is probable that irreversible anatomical changes had occurred which could be corrected only by surgical measures.

The whole problem of the endocrinology of prostatic hypertrophy continues to be most perplexing. There is no agreement concerning the details of the nature of the disease. Parkes[10] feels that the disease is due to an imbalance between estrogenic and androgenic hormones and for this reason advocates the use of testosterone. Van Capellen[11] was probably the first to attempt this form of treatment. His success was comparable to that which we observed when feeding an amount of testicular material which contained only traces of testosterone. Several other workers have since had similar results[12]. Further researches concerning the functional condition of the endocrine system will be necessary before an adequate explanation of this disease will be forthcoming.

The Diagnosis and Treatment of Hypogonadism in the Male

E. P. McCullagh[13] has reviewed some of the literature on hypogonadism in males and has reported cases of testicular deficiency which have been treated with testosterone propionate in this institution.

In prepuberal hypogonadism, i.e., patients who have never shown signs of adequate testicular function—the growth of facial, axillary, and pubic hair is retarded, penile and scrotal development is poor, epiphyseal closures do not occur at the usual ages, and laryngeal maturation is interfered with. These individuals excrete only small quantities of androgenic material in the urine. Treatment with testosterone propionate results in penile growth accompanied by nocturnal emissions and increased production of semen. There is scrotal growth and prostatic enlargement, the latter change showing some lag. There is an increase in pubic and axillary hair and maturation of the larynx.

When gonadal failure occurs after puberty, the anatomical differences between the normal and deficient individual are not as marked as in prepuberal hypogonadism. The deficiency usually manifests itself by decreased libido and potency, which is frequently accompanied by nervous and vasomotor symptoms and decrease in the size of the prostate. The urinary excretion of androgens is decreased. Even in castrates, however, there is usually some androgenic material in the urine. This indicates obviously that there is some source of urinary androgens in addition to the gonads.

Observations made in this institution and the studies of others have shown the symptoms of gonadal failure in the adult can be completely relieved by adequate treatment with testosterone propionate.

The Endocrine Control of Spermatogenesis

Moore[14] has shown that under certain circumstances androgenic materials are injurious to the spermatogenic elements of the testes. Moore and Price[15] have demonstrated by the use of normal rats the fact that over a fairly wide range of dosage of testosterone propionate the testicular damage shows an inverse relationship to the dose, i.e., the greater the dosage the less the damage. Hypophysectomy causes rapid cessation of both the endocrine and spermatogenic functions of the testes.

In our laboratories it has been demonstrated that normal spermatogenesis can be maintained by the injection of androgens into hypophysectomized rats. Nelson and his co-workers[16] have confirmed this and have demonstrated that such treated animals could sire normal litters. If, under these circumstances, the testes are permitted to become atrophic, the pituitary hormones will cause their restoration but the androgens are ineffective.

Cutuly, McCullagh and Cutuly[17] studied the efficacy of various androgens in the maintenance of spermatogenesis and found that testosterone and testosterone propionate are among the least efficient. McCullagh[18] suggests that other androgens are normally formed in the testes and that the existence of these other substances accounts for the normal maintenance of spermatogenesis.

We have also demonstrated that testosterone propionate has a very potent influence as a depressor of the gonadotropic function of the pituitary gland. This no doubt accounts for the fact that small doses cause profound damage to the spermatogenic elements of the testes. Dr. E. P. McCullagh in the Department of Endocrinology is at present studying these effects in the human, and there is every reason to believe that the results will parallel those seen in experimental animals. This means that in partially hypogonadal men the treatment with testosterone propionate may have a deleterious influence over whatever spermatogenic function they have. This would suggest that when attempting to stimulate the sex functions by the use of androgens, some substance other than testosterone propionate should be employed if one desires to maintain spermatogenesis.

Testicular Transplants

When patients suffering from hypogonadism are treated with testicular hormone, their functional response is usually largely lost if replacement therapy is discontinued. This of course is usual in endocrine replacement therapy. It would seem that the successful glandular transplantation would be more to be desired than the continuous administration of endocrine products. Therefore, in spite of the well known difficulties involved in the transplantation of human tissues, we have undertaken a reinvestigation of the subject of testicular grafts.

The study of the physiological effects of transplantation of the testes extends back many years. John Hunter is credited with first transplanting testes from one animal to another. This was about the middle of the eighteenth century. Foa[19] attempted to transplant the testes into the scrotum but had negative results. The first to attempt to transplant the testes of young rats into the scrotums of older castrated animals were Castle and Phillips[20]; negative results were obtained. C. R. Moore[21] first obtained perfectly differentiated spermatozoa in testes grafts residing in the scrotum. In no other location did this occur. Moore's work revealed that testes grafts residing in the scrotum gave a very poor percentage of takes because of poor vascularization. Furthermore, his grafts which were recovered from subcutaneous, intramuscular, or intraperitoneal positions revealed good interstitial cell development but relatively poor tubule development.

The research department of the Cleveland Clinic Foundation has been

investigating the factors involved in successful testes transplantation as well as their physiological effects. This experimental work has been done chiefly upon rats. Under our direction, Dr. Eugene Cutuly, formerly of this laboratory, selected the ear of the rat as a possible favorable location for testicular transplants, first, because the rat's ear might offer adequate vascularization and, second, the ear might supply the temperature necessary for the development of the spermatozoa.

The experimental results obtained in studying the organs of rats with transplants are given in table 1. The organ weights are expressed in

TABLE 1

MAINTENANCE OF NORMAL ORGAN WEIGHTS BY A SMALL TESTICULAR TRANSPLANT

	Average Body Weight	*Average Weight of Organs Expressed as Mgm. per 100 grams of Body Weight*			
		Pituitary	*Testes*	*Seminal Vesicles*	*Ventral Prostate*
10 Normals	226	2.1	1370	240	68
6 Castrates with testicular transplants	295	2.7	54 (Transplant)	274	120
6 Castrates	207	4.6		4.1	5.5

milligrams per 100 cc. of body weight, which we believe makes the comparisons more valid than a direct comparison of organ weights when the animals are not all of the same size. The pituitary glands of castrated rats with transplants in the ear are almost normal in size and do not show the marked hypertrophy which occurs in the glands of castrated rats which have no transplants. The efficacy of transplanted testicular tissue in maintaining the secondary sexual organs is very evident. The transplants are only about 4 per cent of the size of the normal testes. The secondary sex glands, however, of the castrated animals with transplants are larger than the same organs in normal animals, whereas those which had no transplants had infantile secondary sex glands.

These researches are an extension of earlier investigations in other laboratories. Fischera[22] concluded that the pituitary gland enlarges to about twice the normal size after castration. Our results show that the increase in the pituitary weight in the castrated rats is slightly above this 100 per cent increase. Libschütz et al[23] revealed that only ten per cent of the normal testicular tissue is necessary to maintain the secondary sex characteristics. This is comparable to our findings that a trans-

plant weighing 4 per cent of the weight of normal testes will maintain the secondary sex glands.

Summary

1. Animal experiments demonstrate that the pituitary, the testes, and the prostate are closely interrelated. Clinical investigations have demonstrated that this is also the case in man.

2. Clinical prostatic hypertrophy is frequently a disease of endocrine origin. The symptoms have been relieved in some instances by the use of testicular preparations.

3. The pituitary gonadotropic hormone and the androgens both play a rôle in spermatogenesis.

4. Useful laboratory methods have been developed to aid in the diagnosis of endocrine disorders of the testes.

5. When the production of androgens is deficient, the urinary androgens can be brought back to normal by the administration of substances such as testosterone propionate; symptoms of hypogonadism are relieved by this treatment.

6. New laboratory experiments concerning testicular grafts are reported.

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The annual meeting of the American College of Physicians will be held in Cleveland, April 1-5, 1940. The Bunts Course, usually given in the spring, will not be offered this year to avoid a conflict in meetings.

ESOPHAGOSCOPY

Treatment of Lesions of the Esophagus

PAUL M. MOORE, JR., M.D.

Practically all lesions of the esophagus have one outstanding symptom in common,—dysphagia—and it is because of this that patients seek the advice of a physician. The name esophagus is derived from the Greek and means to carry food. This is its sole function. Any lesion which interferes with its normal function produces dysphagia. A puncturing injury or an ulcerating lesion may lead to mediastinitis, a tracheo-esophageal or broncho-esophageal fistula or to a fatal hemorrhage.

The only ways by which the esophagus may be visualized are by the use of the roentgen rays and barium meal and by the use of the esophagoscope. The first should always be used. In the majority of cases this should be supplemented by esophagoscopy. Esophagoscopy has a two-fold use. First, it is a diagnostic aid of proved value. By its use the entire length of the esophagus can be inspected, and lesions which may be too small to be visualized by roentgen examination can be seen. Biopsy specimens can be removed for pathologic examination and diagnosis. Secondly, it can be used for treatment. The most important use in this respect is the removal of foreign bodies. Local treatments can also be given when they are indicated.

The procedure is attended by little danger when it is done by a careful and experienced operator. Rough handling and the use of too much force may produce a rupture in the thin wall of the esophagus and lead to a fatal mediastinitis. The point where the greatest care must be observed is at the very beginning of the esophagus where it is kept closed by the contraction of the cricopharyngeus muscle. A spasm of this muscle must be overcome by gentle pressure but it cannot be forced. The presence of a sharp pointed or edged foreign body carries grave danger of perforation and mediastinitis, and its removal must be accomplished with the greatest care.

Contraindications for use of the esophagoscope are aneurysm, advanced organic disease, extensive esophageal varicosities, and acute esophagitis.

In performing esophagoscopy, the patient is given preoperatively a hypodermic of morphine and atropine. A local anesthesia of cocaine or pontocain is used. No pain is associated with the procedure but there is some discomfort. It is a great help if the patient is relaxed and not nervous and tense.

Among the *congenital abnormalities*, one in particular can be treated through the esophagoscope. This is the case with webs across the lumen of the esophagus. These webs can be cut or removed and thus result in an unobstructed passageway for food. If a stricture is present, it can be

treated by dilations. The whole subject of dilating the esophagus and the various methods used will be discussed later.

In the pulsion type of diverticulum, the esophagoscope can be a valuable aid to the surgeon who is to remove the sac. Preoperatively, it can be used to clean the sac and to clear up any infection which is present. It is often inserted into the sac at the time of operation to help the surgeon locate it and to determine its size and extent.

Foreign Bodies: There is usually a history that the patient has swallowed a foreign body and that this was followed by more or less dysphagia. In the case of an infant who has been playing among an assortment of toys and who is not under the watchful eye of an elder, this history may be missing. The only thing that is noticed is that the child has difficulty in swallowing or refuses food. There may be an associated cough. The infant becomes listless and if forced to take food, regurgitation may occur. Any infant showing such symptoms should be suspected of having a foreign body in the esophagus. It is well to remember that the roentgen examination may give negative findings if the foreign body is not radio-opaque. The barium meal and esophagoscopy should be used. One infant who was admitted to the University Hospital at Ann Arbor while I was an interne made a lasting impression on me. It had been months since the child had first shown signs of sickness. During this time, he had been observed and treated but a roentgen examination had not been made until just before he was sent in. The roentgenogram showed two safety pins in the upper end of the esophagus. When removal was attempted, these were found to be deeply imbedded in the wall of the esophagus. Removal was followed by mediastinitis and death.

Another example of the disastrous result of neglecting a foreign body is shown by the following case. A 14 year old girl swallowed a chicken bone which lodged in the esophagus. On the assumption that it might pass on, nothing was done. A few days later she had less difficulty in swallowing and seemed to be all right. No roentgenogram was taken. Several weeks passed. Then severe hemorrhages from the mouth began and she was rushed to the hospital. She arrived in severe shock from the loss of so much blood. She was in no condition for manipulation but transfusions were given immediately and she was treated for shock. She failed to rally and died. At necropsy, the esophagus was found to be filled with blood. The chicken bone had lodged crosswise but was so narrow that it did not cause complete obstruction. There was necrosis of the esophageal wall at either end of the bone. If esophagoscopy had been performed soon after the bone became lodged, an entirely different outcome could have been expected.

Chicken and fish bones are often too small to show in the roentgen films, although it is sometimes possible to find a filling defect by the use of barium. In any case, every patient with a positive history should be

examined with the esophagoscope unless it can be definitely proved that the foreign body has passed on into the stomach or has been regurgitated. In this way tragedies like the above two cases can be averted. It is true that in many cases the small bone scratches the mucosa but does not lodge. This leaves a sensation of pain on swallowing and the patient often feels as though the bone were still in the throat. On examination the mucosal injury is seen and the absence of the foreign body is demonstrated. This requires a very careful and thorough examination because the many folds in the upper end of the esophagus may conceal a small foreign body. There is danger of perforation and mediastinitis when sharp points or edges are present and removal should be accomplished with the least possible trauma.

Whenever possible, a duplicate of the foreign body should be procured. The family should be instructed to bring a duplicate if they possibly can. This enables the operator to make a better selection of forceps and to work out the mechanics of removal before starting the operation.

In the case of globus hystericus and Plummer-Vinson syndrome, the negative findings on esophagoscopy help establish the diagnosis. In carcinoma a biopsy can be taken. Varices can be seen and may be treated by puncture diathermy. Ulcerations can be treated locally in the same way that ulcerations in the mouth are treated.

All patients with cardiospasm (see fig. 1) and strictures (see fig. 2) should have the benefit of esophagoscopy. The diagnosis can be definitely established and the presence of a small inciting carcinoma or ulceration can be ruled out. In the former the findings are characteristic. The esophagus is more or less dilated all the way down to just above the stomach. In cases of long standing the dilation may be very great. At the location of the spasm, the esophagus is tightly drawn together. The Jackson esophageal dilators can be passed gently into the stomach. This dilation is continued until the largest size that can be used has been passed. As soon as the patient has recovered from the immediate effects of the manipulation, he notices a distinct improvement. Subsequent dilations can be carried on without the use of the esophagoscope.

In the case of cicatricial stricture the problem is much greater. These patients have usually swallowed lye or some other corrosive agent. After they have recovered from the burn itself they may be able to eat quite well and the contraction from scar tissue may not be manifested for a period of weeks after the original injury. If seen during this time the prognosis should be guarded because obstruction may develop later on.

Patients with congenital and cicatricial strictures, cardiospasm or carcinoma can all be treated by dilatation of the esophagus. In the case of carcinoma, treatment is merely palliative and is attended by the danger of rupturing through the wall of the esophagus. Dilations should

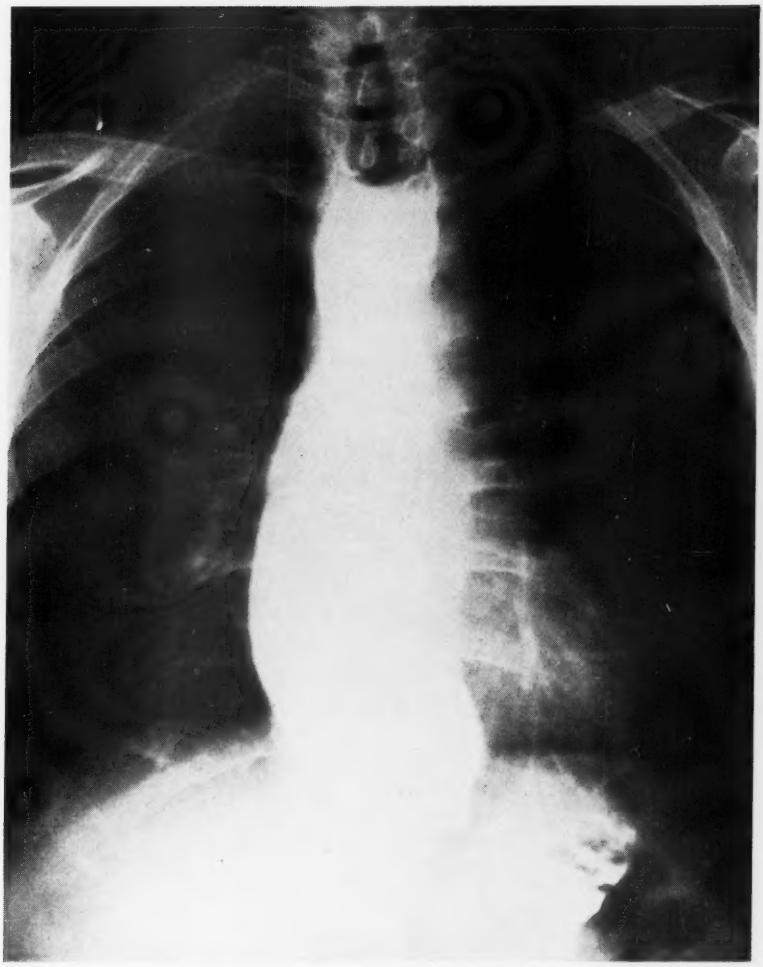

FIGURE 1. Cardiospasm.

be done very gently. The patient swallows a string and this is used to guide the olive-tip dilator. If a gastrostomy is performed so that the patient can be fed directly into the stomach, dilatations are not necessary.

Cardiospasm or preventiculospasm can be treated successfully, and excellent results can usually be expected. The Mosher bag has largely replaced the old Plummer hydrostatic bag. The former is expanded by air, is safer and is more convenient. It has metallic ribs so that the dilatations can be done under fluoroscopy if desired. Another very use-

ful dilator is the graduated flexible dilator filled with mercury. The dilatations should be done at intervals of 2 or 3 weeks, and the intervals should be lengthened as the patient improves. Atropine and a bland smooth diet should be given until the co-existing esophagitis is cured.

Patients with strictures, either congenital or traumatic, require a much longer and more tedious course of treatment. Formerly, dilations from above along guiding strings or under direct vision through the esophagoscope were used, but this method resulted in too many ruptures of the esophagus and complicating mediastinitis. Pockets or small

FIGURE 2. Stricture of the Esophagus.

diverticula are often present above the stricture. When dilations are attempted from above, the end of the dilator may pass into the pocket and be forced through the esophageal wall. The blind use of dilators or bougies to dislodge foreign bodies is also attended by the same danger of rupture of the esophagus. In this case the foreign body may deflect the end of the bougie and cause it to pass through the esophageal wall. If the foreign body has sharp edges or points it may lacerate the wall so that infection may pass through.

The best procedure with stricture cases is to perform a gastrostomy. After this is healed, the patient swallows a string to the end of which has been fastened a small lead shot. When the shot has reached the stomach as shown by the roentgenogram, the string is recovered through the gastrostomy wound. The esophagus is then dilated by the retrograde method. The dilator is fastened to the string and passed through the stomach and into the esophagus. It is allowed to remain in place a few minutes and is then drawn out by way of the gastrostomy wound and a larger dilator is passed. Between dilations nutrition is maintained by feedings through the gastrostomy tube. The string is left in place with the upper end through the nose. This is continued until a size 40 dilator can be passed through the esophagus and until at least a month has elapsed without any contraction of the stricture. Then only is the gastrostomy wound allowed to close. After the esophagus has become pretty well dilated, the patient is allowed to take food by mouth and the string may be removed between dilations, to be reswallowed at the time of the next dilation.

In closing, I should like to mention one more patient whom I saw some years ago. This patient had dysphagia due to an obstruction midway in the esophagus. The first esophagoscopy had been somewhat unsatisfactory but, because of the marked obstruction and loss of weight, a gastrostomy had been done so that he could be fed. A string with the lead shot on the end was then given to him to swallow. The string was to act as a guide for a second esophagoscopy and to be used for retrograde dilation later. Some hours after he had been given the string to swallow, he began to cough violently. When the coughing failed to subside it was thought that he might have aspirated the string instead of swallowing it. An attempt to pull the string out through the mouth showed it to be firmly held in place. Examination with the laryngoscope showed the string to be leading down into the esophagus. But it also showed a string leading into the larynx and trachea. He had a tracheo-esophageal fistula, had swallowed the string but it had passed through the fistula into the trachea. His coughing had blown the bead and string attached to it up through the larynx where it had become entangled with the other portion of the string and had tied itself in a knot. The string leading into the larynx had to be cut before it could be removed.

FRAGILITAS OSSEUM. BRITTLE BONES AND BLUE SCLERA. HEREDITARY MESENCHYME HYPOPLASIA

B. H. NICHOLS, M. D.

I have seen recently at the Clinic a case which I consider to be a mixed picture of fragilitas osseum, osteitis fibrosa cystica, and Paget's disease, which began with blue sclerotics and brittle bones. I believe this supports the theory that these lesions have a general relative etiology, and the findings in this case demonstrating various stages of the same disease indicate that it is not due to parathyroid disease.

CASE STUDY

The patient was a man 31 years of age when admitted to the Clinic. He had been a normal child until at the age of 7½ years when the skull became abnormal in shape and the left maxilla became enlarged. He had a series of fractures beginning at the age of 17 years, which occurred with slight trauma and continued until the age of 24 years. He broke

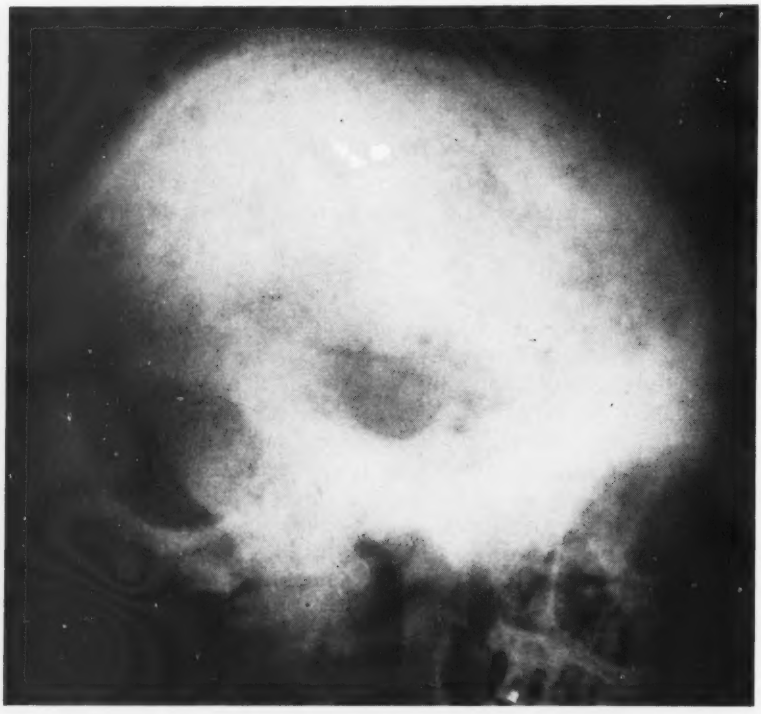

FIGURE 1A. This skull represents the usual findings of a Paget's disease.

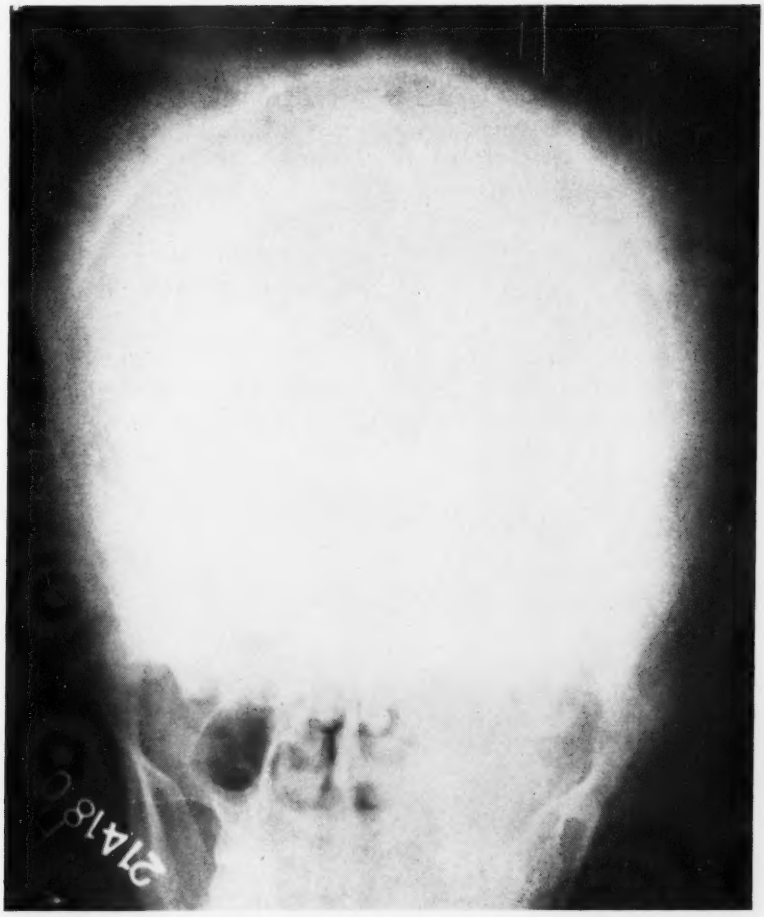

FIGURE 1B. A posterior anterior view of the same skull as in 1A.

ribs by sneezing and putting on his shirt. He fractured the sternum in a friendly boxing bout. He has fractured both clavicles and the right femur by insignificant trauma. He has had pains in the leg and many "painful bones." There has been frequent nasal bleeding.

Physical examination revealed a man 63 inches in height and weighing 122 pounds. He was poorly developed and had blue sclerotics. He had had some dental extractions but the remaining teeth were excellent. There was marked pigeon breast deformity and scoliosis of the right mid-dorsal region. A systolic murmur was heard. The examination of the abdomen gave negative findings. The left maxilla and entire cranium

were markedly enlarged, and the patient wore a size 8 hat. There were large parietal bosses. The skull was deformed from left to right and there was marked enlargement of the left mastoid process. Although the joints were freely movable, he had a marked deformity of the fibula due to bony exostosis and lumbar lordosis. The right leg was 4 cm. shorter than the left. Bony exostoses of the left ear canal were present and hearing was diminished in the left ear. The skin showed moderate pigmentation.

Clinical diagnosis: Osteogenesis imperfecta tarda and leukodermo.

Laboratory: Preoperative blood calcium 9.6-13: Phosphorus 1-3. Phosphatase was five times that of normal.

Operation: One parathyroid, which was 2½ times that of normal size, was removed at operation. The remaining parathyroids were normal.

Pathologic sections: Pathologic sections revealed a normal parathyroid.

FIGURE 2. The pelvis and upper femurs show the typical cyst formation as seen in osteitis fibrosa cystica. There has been an old pathologic fracture in the upper right femur.

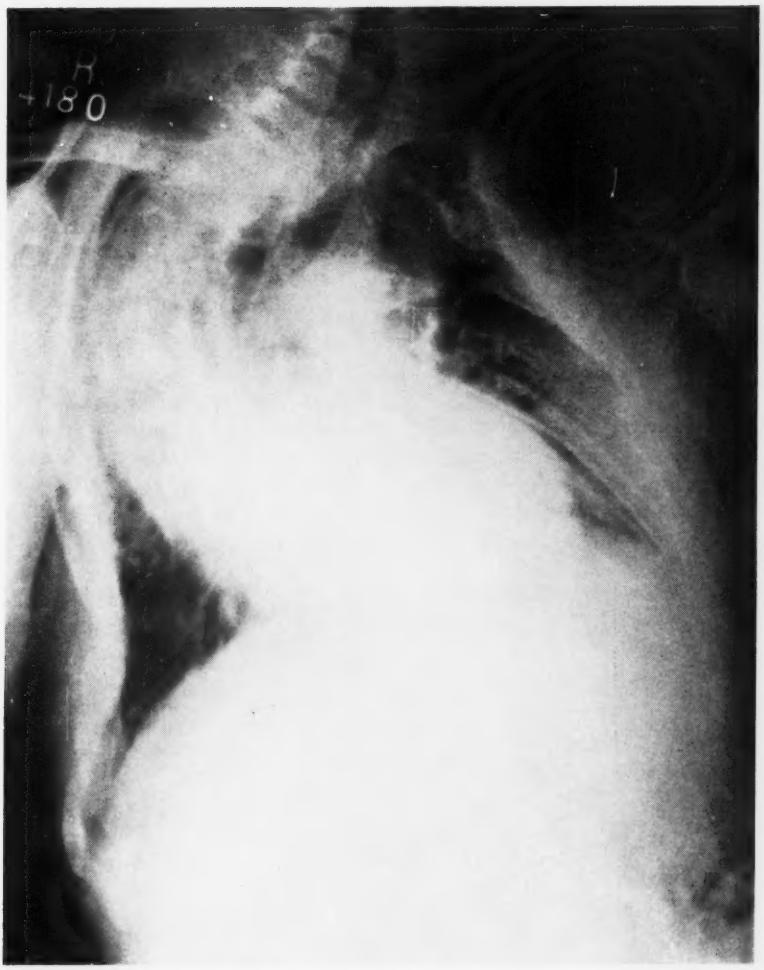

FIGURE 3. The dorsal spine shows marked right dorsal scoliosis, and cystic formation in the ribs.

Convalescence was uneventful except for slight Chvostek's sign which disappeared in three days. On postoperative examination calcium was 8.75. The patient was discharged 8 days after the operation. One month later the blood calcium was 9.6; phosphorus 3.22. The patient was feeling well and stated that he had no pains.

Eight months after the operation the blood calcium was 10.1 mgm.; phosphorus, 3.71 mgm. The patient stated that he was freer of pain and was enjoying better health than ever before. A month after this

visit, nine injections of endocalcium chloride were given intravenously elsewhere. The patient developed pains around the sternum and ribs. However, after cessation of injections the pain subsided but left residual burning around the sternum.

A week later a comparison of roentgenograms showed no advancement of the process although Dr. E. Perry McCullagh thought it apparent that some areas had improved.

A letter received from the patient nearly 10 months following operation stated that he was practically free of pain and fractures since parathyroidectomy.

However, a month after the first communication, another letter from him stated that he had dyspnea and decreased vitality. The blood calcium was 10.1; phosphorus, 3.1. The patient was morbid about his condition, wanted his money back and said his "bones felt as bad as ever." Four months after this, he stated that he had no pains, felt well and had no fractures. Roentgenograms showed no increase in lesions. The calcium was 9.7; phosphorus, 2.27 and phosphatase 4.81 (increased). Then, in three months, a large cystic formation of the left femur developed and he was unable to walk and had severe pain. Cal-

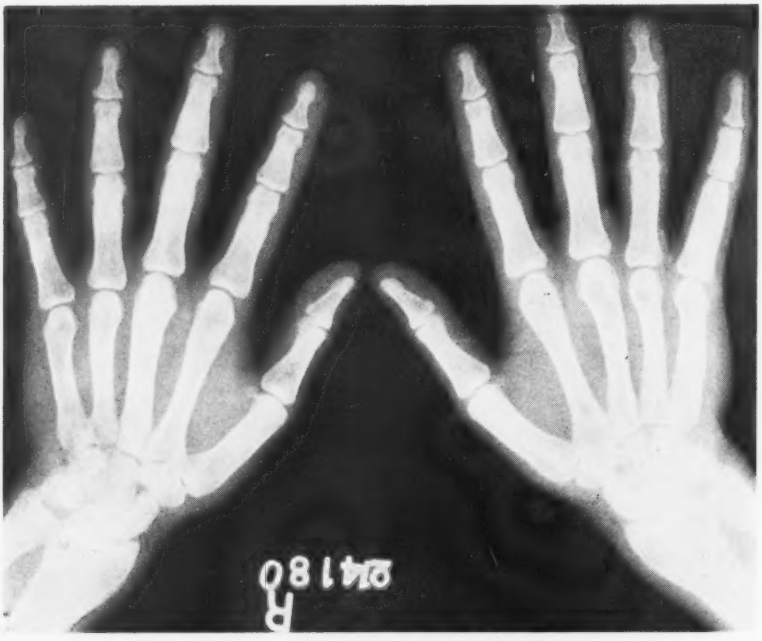

FIGURE 4. The hands which formerly showed considerable generalized malacia are now much improved.

FIGURE 5. There is rarefaction of the malacia type in the bones about the knees.

cium at that time was 9.3 and phosphorus 2.7. Three weeks later the patient was in a wheel chair due to the large cyst of the left femur. Then followed a pathologic fracture which after four months showed very little callus. Eight months after the facture he was still confined because of it. Phosphatase (Bodanski) was 4.25; calcium 9.2.

The following year exploration of the parathyroids was done but revealed no abnormality. Following this examination, marked improvement was noted in subjective symptoms even though no parathyroid or parathyroid tissue was removed. Fatigability had diminished and pain in the legs disappeared. Roentgenograms showed no change in the bones. Serum calcium was 9.5-12.5; phosphorus 2.9-3.4; phosphatase 21.5-28.2 (Bodanski). The basal metabolism was +7 per cent. Chronaxia was normal with a definite negative calcium balance.

Painless fractures continued with slight trauma until the patient became hopelessly discouraged. Two months after the exploratory operation he broke a rib by lying in an awkward position in bed.

This case was reviewed by Dr. I. Seth Hirsch[1] in which he makes the following comments on the roentgen examination:

"X-ray examinations of this patient have been made at three distinct periods during the past 15 years. In a general way, therefore, it may be stated that the lesions in the metacarpals and phalanges have shown a tendency to repair in the last 15 years and that no new lesions have appeared. In other words, it would appear that the activity of the lesions in the hands had already ceased at the age of 16. This is borne out by a comparative study of the other bones. There is one exception, however—the skull. Here the changes have been progressive."

In 1913 the following report was made on the cranial bones. They were markedly thickened, especially the frontal and occipital and superior maxillary bones. The differentiation between the tables and the diploe was lost over the frontal area but could be made out in the rest of the bones. The occipital bones, however, showed numerous cystic areas running parallel with the curvature of the bone. The left superior maxillary and the anterior region of the left side was occupied by a bony mass consisting of irregularly formed lamellae of increased density with widened intra-lamellar spaces. The entire base of the skull showed these productive changes.

The sella turcica was very small and its walls were thickened. There was an upward displacement of the posterior portion of the base of the skull, particularly in the region of the foramen magnum. With increasing age, the skull changes in this case progressed until the entire skull was involved, leaving the inner table distinctly clear, but with irregular masses of bone scattered throughout the widely thickened cranial bones. The pelvic bones in 1931 showed cystic areas in both the iliac bones, in the wings, and in the sacral portions. There were large cystic areas in the ischium and pubis without bone expansion, however.

Following a period from 1913 there was considerable increase in extent of the cystic change with little evidence of healing. The patient showed an old oblique fracture at a point two inches below the lesser trochanter with repair in a somewhat deformed position. There had been a pathological fracture through this cystic area, involving the right femur. The spine showed a definite marked lateral curvature with some cystic changes in the vertebrae. The ribs also showed expansion with cystic involvement. The right humerus was involved and extensive cystic changes in the right scapula were noted. Dr. Hirsch comments on the fact that this case is by no means unique and cites references in the literature where a protuberance in the facial or skull bones in young individuals has directed attention to this disease which gradually progresses to complete general bone involvement. His opinion of this case was that it was one of generalized osteitis fibrosa of cystic metaplastic malacia type.

FRAGILITAS OSSEUM

A report recently received from the United States Marine Hospital on Staten Island, New York, makes the following report on this patient. His death occurred in the Marine Hospital eight years after he had first been seen at the Clinic. No necropsy was performed. The cause of death was given in this communication as one of hyperparathyroidism and osteitis fibrosa cystica. This case was followed in the Clinic by Dr. E. Perry McCullagh as a probable case of parathyroid disease with accompanying cystic bone degeneration. I am reviewing this case, however, with the history of early fragile bones and fractures.

The following points might be stressed as in favor of a fragilitas osseum:

1. Normal birth and a normal childhood to 7½ years.
2. Blue sclerotics.
3. Exostoses of the middle ear.
4. Osteosclerotic deafness in early adult life.
5. Absence of optic atrophy.
6. Small stature.
7. Easily fractured bones with prompt healing during childhood, the fractures decreasing with age and with increased healing time.
8. Free motility of the joints.
9. Calcification in the vestibular area.
10. Normal range of blood calcium to an increase of calcium to slightly above normal.
11. Eccentric atrophy of the long bones, with slightly striated cortex of these bones.
12. Carpal bones also rarefied with particular rarefaction at diaphyseal ends.
13. Many pathological fractures.
14. No bending of the long bones.
15. Slender ribs.

Points in favor of an osteitis fibrosa cystica are as follows:

1. Thickening of the jaw.
2. A progressive Paget's disease of the skull.
3. Multiple cystic formation.
4. Pains in the legs.
5. Spinal shortening.
6. Disturbed calcium balance.
7. Tendency of the ribs to fracture.

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PULMONARY ASPERGILLOSIS

With Report of a Case

By H. Scott Van Ordstrand, M.D.

Classification

Pneumomycoses are among the most interesting non-tuberculous chest diseases because of their relative rarity. Aspergillus lung infection is one of the more common forms of mycotic infestation of pulmonary tissue. Of the thirty-seven better-known strains of aspergillus, fumigatus and niger seem to be the only pathogens. Aspergillus fungi are classified as members of the filamentous group and are practically ubiquitous in nature.

Castellani[1] has classified fungi (which may produce lesions simulating pulmonary tuberculosis) as follows:

1. "Yeast-like" fungi	Blastomyces
	Cryptococcus (torula)
	Saccharomyces
	Monilia
	Endomyces
2. Filamentous fungi	
a. Slender type	Nocardia
	Anaeromyces
	Vibriothrix
b. Larger type	Oidium
	Hemispora
c. Types with characteristic conidial structures, fructifications, etc.	Aspergillus
	Penicillium
	Mucor
	Rhizomucor
	Acrimoniella
	Sporotrichum
	Acladium

History

Pneumomycosis was first described by Hughes Bennett in 1842. In 1853 Rayer and later Gairdner described cases of pulmonary tuberculosis in which the pleurae were invaded by a fungus. Virchow, in 1856, described several cases of aspergillary mycoses of the lungs and bronchi. Dieulafoy, Chautmesse, and Widal in 1890 described clinically several cases of pulmonary aspergillosis occurring in persons who were engaged in fattening pigeons for the Paris market, and they advanced the idea that the infection was a primary one.

In 1897 Renon brought forth a very complete monograph on the subject, experimental as well as clinical. He considered it to be a trade disease among those undertaking the artificial feeding of pigeons and those manipulating hair and hair products. He believed the disease to be rare outside of Paris. The infecting agent he elucidated as asper-

gillus fumigatus and rarely, aspergillus niger, spores of which may be mingled with grains, seeds or flour.

Mary Lapham[2] in 1926 reported ten cases of primary pulmonary aspergillosis from an obscure village in the Blue Ridge Mountains, and divided the cases into two groups: the wet or parenchymatous types, and the dry or interstitial types. She also called attention to a definite relation to asthmatic attacks in certain cases. Pinta in 1935 reported asymptomatic cases found in Oklahoma, during a routine chest examination of workers in iron mines. Wheaton's case, a child of thirty months, is the youngest recorded instance, and Virchow's patient, who was seventy-seven years of age, the oldest example.

The genus Aspergillus, first described in 1725 by Micheli, belongs to the family Aspergillaceae, order Aspergillales of class Ascomycetes. It is a regular inhabitant of the soil, at least in America, and is one of the most abundant molds encountered. It has been frequently isolated from cereal products, unmilled grain, hay and other stock feeds. As an agent of disease it selects for its victims chiefly certain species of birds, particularly the pigeon, but also canaries, penguins, ducks and chickens. Among mammals, dogs and cats are said to be insusceptible to its spores, but lesions have been produced experimentally, in rabbits, guinea pigs, monkeys and others.

The majority of writers supports the view that as far as man is concerned, healthy individuals are relatively immune to aspergillus[3]. It could hardly be otherwise if the race were to survive, in view of the boundless opportunity for contact with this organism in nature. Accordingly, because man is susceptible to the disease caused by this organism, one is led to recognize the possibility of particular predisposing conditions.

As mentioned before, the classic instances of pulmonary aspergillosis in man are found in certain occupations which involve prolonged and intimate contact with grains or with birds. Farmers, feed-mill workers and threshers are prone to this infection. The most frequently quoted example is that of the pigeon-stuffers of the suburbs of Paris who, with their own mouths, cram the beaks of the birds with a mixture of grains and water, many workers averaging from four to six thousand such gavages a day. Some of them develop a rather severe type of mycotic pseudo-tuberculosis with the double hazard of infection from the grain and from the infected birds.

Certain dusts are important sources of infection, such as that produced by sponge-cleaners who beat the dried sponges, and by the wigmakers of Paris who comb the hair with rye meal to remove the fat, the air in some of these establishments being practically unbreathable. In all of these instances it is probable that massive dosage, often repeated,

is the principal factor in the pathogenesis of the disease. Symptoms of infection in such cases may be long in making their appearance, and, even in cases severely afflicted, may disappear completely upon removal of the patient to another environment and occupation.

Under other circumstances, the factor of constitutional or of local predisposition is the determining one, and this has brought about the concept of "secondary aspergillosis." Uncontrolled diabetes has been cited as predisposing to pulmonary aspergillosis with massive necrosis of the lung. Fuerberinger has listed carcinoma, dysentery, enteritis, cirrhosis of the liver, and sepsis as additional predisposing factors. Grippe in a patient with latent pulmonary aspergillosis has been shown to excite a rapidly advancing necrotizing lesion. Many writers, particularly Wahl[4], have emphasized the frequency of this disease as a secondary invader in tuberculosis, and vice versa. Allergists are well aware of the frequency of aspergillus sensitivity in asthma and allergic rhinitis, with failure to cure often occurring if treatment does not include desensitization to these offenders.

Most pathologists describe the disease as roughly falling into two characteristic groups, a "superficial" and a "deep" form. In the former are included cases of bronchitis, catarrhal or asthmatoid, which run a fairly benign course. The "deep" or ulcerative type depends on the ability of the endotoxins of the mold to cause necrosis of lung tissue analogous to caseation as in tuberculosis. These distinctions between the two types are relative and vary also with the degree of the allergic component of the inflammatory response of the tissues or their disposition to undergo fibrosis. Experimentally, using rabbits, Henrici[5] has demonstrated well the lesions of the Aspergillus fumigatus and has shown that they have a high and constant virulence for laboratory animals. When spores from a young culture were inoculated intravenously, the type of disease produced varied with the dosage. With large doses, the animals died within a day or two, presenting only hemorrhages and necrosis about the germinating spores which had lodged in various tissues. With smaller doses, the animals survived two to seven days, with resulting miliary abscesses. With still smaller doses, the animals survived ten days or longer, the lesions developing into tubercles, resembling those produced by the tubercle bacillus.

Symptoms

The symptoms of pulmonary aspergillosis may be of acute or chronic nature. The acute form assumes clinically the picture of bronchitis or pneumonia. The bronchitic type has its onset in a manner not unlike the ordinary upper respiratory infections or common cold. The symptoms persist, however, with low grade fever and paroxysms of coughing productive of a minimal amount of tenacious mucoid sputum. The physical findings in this group are usually very meager, showing at most only a

few coarse hilar râles. The pneumonic form of acute onset simulates other pneumonias with the associated dyspnea, cyanosis and chills and moderate degrees of fever. The dyspnea may be most marked nocturnally, and occurs in paroxysms as does the cough. In acute cases, hemoptysis may be an early symptom, followed by fatigue, anorexia and loss of weight. Night sweats may be a very prominent symptom.

The course of chronic primary aspergillosis is similar to that of chronic pulmonary tuberculosis. There may be a history of recurrent attacks of pleurisy extending over a period of years. Symptoms of malaise, morning cough and undernutrition may have been present for a long duration of time. Cough with progressive dyspnea on exertion becomes more distressing as the disease progresses. The cough becomes more productive and the sputum more purulent as areas of parenchymal excavation occur.

Most authorities agree that the changes produced in the lungs by early aspergillosis, and for all pneumomycoses, cannot be differentiated roentgenographically from pulmonary tuberculosis. There may be no demonstrable lesion in early cases. When roentgen changes do occur, the infiltration is prone to be basal[6] in location, thus further confusing the roentgenologist. Many and varied roentgen appearances have been described. Probably the more nearly typical roentgen picture is the increase of hilar shadows with radiating spider-web appearance (as seen in figure 1 of the case report), which Sampson has appropriately called the "sun-burst" effect. Kindberg, Parat and Netter[7] have reported a case resembling a tumor which they have classified as primary pseudocancerous aspergillosis.

The possibility of pulmonary mycosis should be considered in everyone having pulmonary symptoms. The diagnosis of aspergillosis is made only after finding the fruiting spores in the sputum along with careful exclusion of all other possible etiologic factors. The fruiting heads of the fungus must be found on smear or hanging drop examination. Reproduction of the lesion with animal inoculation and with reisolation of the fungus is of added support in establishing the diagnosis. A positive agglutination of the patient's serum on the suspected type of aspergillus, as well as a positive skin test with a stock extract or autogenous vaccine of the fungus will be added presumptive evidence. A positive culture alone is not considered sufficient evidence to warrant the diagnosis.

Various agents have been used in the treatment of pulmonary aspergillosis. Potassium iodide is time-honored as a remedy for this disease, as it is for many of the other mycoses. David Smith has emphasized desensitization to an extract of the fungus when marked skin sensitivity is found, prior to the use of iodides. Some men feel that inhalation of

ethyl-iodide is preferable to the oral use of iodides. Arsenicals, especially in the form of neoarsphenamine, intravenously, have proved to be very efficacious in some hands. Some also advocate the added use of intramuscular bismuth. Thymol is gaining wider use and may prove to be of considerable value. The multiple therapy employed in this disease emphasizes the lack of a "specific" drug.

Case Report

A thirty-six year old nurseryman came to the Clinic on October 26, 1939, with the complaint of a "chest cold which will not clear up." He described the onset three weeks previously as consisting of nasal obstruction with rhinitis and sore throat. Soon after the onset, he began to note daily fever and general malaise in the early evening, persisting through most of the night, and associated during the night hours with paroxysms of coughing and drenching sweats. The temperature would average 102° Fahrenheit at midnight. The coughing was productive of only a small amount of thick, tenacious, mucopurulent sputum. Anorexia was noted in the three days prior to entering the Clinic. There had been a six pound weight loss.

Nothing of significance was recorded in the past, personal and family history and the system review was non-contributory. The only significant finding on general physical examination was the presence of a few coarse crepitant râles near the hilar regions in both lung fields. The morning temperature was 98.6° Fahrenheit. Nose and throat examination with irrigations of the antra revealed no significant findings. Sinus roentgenograms revealed a small cyst in the left antrum. The remainder of the general physical examination revealed entirely normal findings.

Stereoroentgenograms of the chest (figure 1) revealed a proliferative infiltration of moderate degree extending out from each hilum into the middle and lower lung fields. This infiltration had much the appearance of spider-web or sun-burst pattern.

The intitial sputum specimen revealed numerous sprouting mycelial spore formations of aspergillus fumigatus on unstained wet coverslip preparation. These were better demonstrated in hanging drop after emulsification and digestion of equal parts of the sputum with equal parts of 4 per cent sodium hydroxide. Implantation of the sputum on Wort agar revealed growths of aspergillus fumigatus in all tubes, one tube containing a pure culture. Sputum examination was negative on smears and cultures for all other pathogenic organisms. Rabbits, inoculated intravenously with one cc. of sputum revealed multiple visceral mycotic nodules when autopsied in seventeen days. Unstained and stained smears, after crushing these nodules, revealed mycelial formations. Cultures of these mycotic abscesses produced a pure growth of the Aspergillus fumigatus.

Skin tests on the patient, using both a stock as well as autogenous extract of the Aspergillus fumigatus, were positive. The tuberculin test was negative. A sera-agglutination of the fumigatus spores was attempted with a questionable result, due to the tendency for the spores to clump together in any solution.

In the other laboratory studies, the blood sugar and blood counts were normal and the Wassermann and Kahn reactions of the blood were negative. Urine specimens revealed a one plus degree of albumin, but were

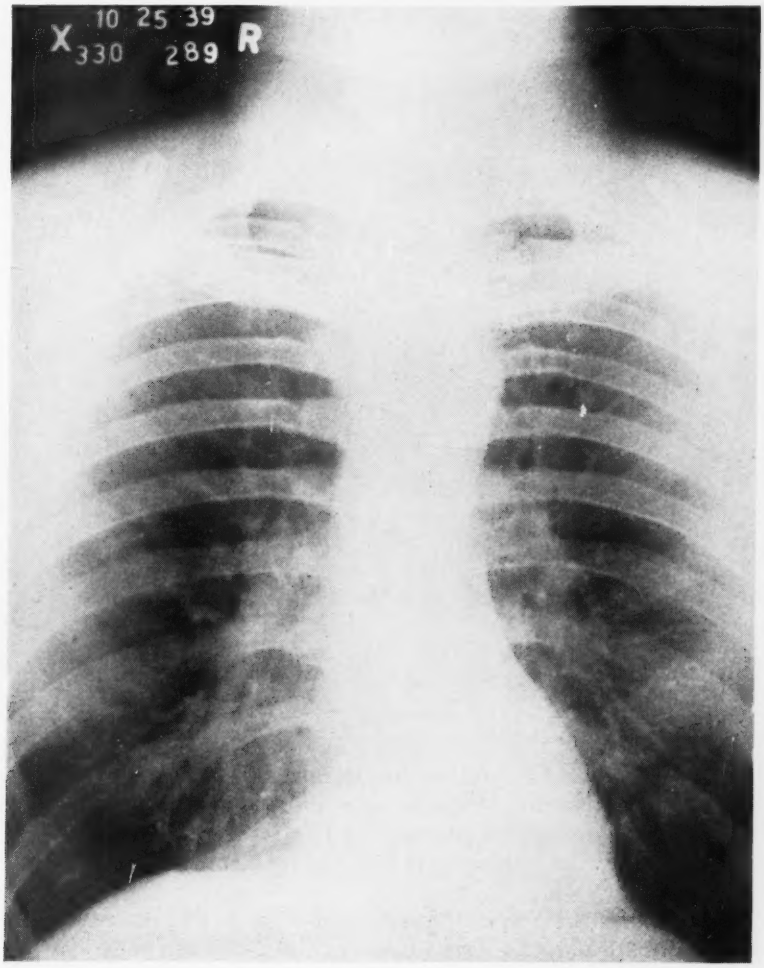

FIGURE 1: Roentgenogram taken at time of initial examination, showing the parenchymal infiltration extending from each hilum.

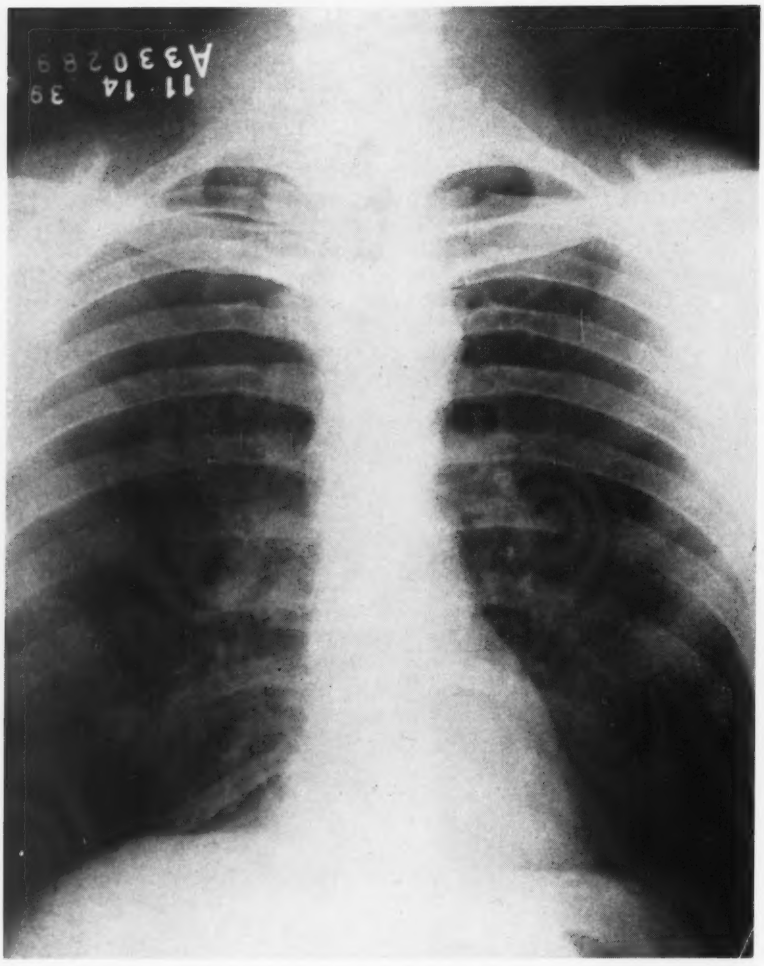

FIGURE 2: Roentgenogram taken twenty days after institution of treatment, showing a considerable clearing of the infiltration.

otherwise negative. The erythrocyte sedimentation rate was elevated to three times the normal. Undulant fever immunity was evidenced by a positive skin test to bacillus abortus, negative agglutination and the presence of 100 per cent phagocytosis in the opsonocytophagic index determination.

Treatment consisted of oral iodides and thymol. The patient became symptom-free within two weeks time and has remained so to date. A chest film (figure 2), taken nearly three weeks after treatment was instituted, revealed much clearing of the parenchymal process.

Summary

Pneumomycosis should be considered as a possibility in anyone having pulmonary symptoms. The history and development of our knowledge concerning aspergillosis is a fascinating subject.

The symptomatology, physical and roentgen findings are discussed. In diagnosis, the necessity of demonstrating the active fruiting heads of the fungus as well as the need of careful exclusion of other similar diseases, is stressed.

A case of Aspergillosis fumigatus of the acute "bronchitic" type is presented.

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INTUSSUSCEPTION IN ADULT

J. C. Root, M.D.

Intussusception is one of the infrequent etiologic factors which must be considered in those patients seen with an intestinal obstruction without other apparent cause. The frequency with which it may occur diminishes with the increasing age of the patient to adult life. Most of the cases of this condition are, of course, seen in the infant. In our experience it is very uncommon in the adult; we have seen but two cases in the last 4000 gastro-intestinal examinations. However, this is not a true criterion of the frequency, since both of these occurrences were fairly longstanding and there is little doubt that chronic cases occur less frequently than do the acute manifestations.

This condition must not only be considered as a cause of intestinal obstruction but must also receive careful consideration in the differential diagnosis of certain cases of suspected neoplasm. The following case illustrates very well the importance of considering intussusception, not only from the point of intestinal obstruction but also to be differentiated from a neoplasm.

Case Study

The patient, a 59 year old man, had always been in good health until four months ago when he began to notice epigastric distress after meals. Gradually there developed cramp-like, colicky pains in the abdomen and he noted a hard lump in the right lower quadrant. He was unable to eat because to do so aggravated the cramps. At the same time he became constipated, which increased in severity so that it became necessary to take castor oil for relief of the abdominal cramps. Blood was noticed in the stool on two occasions, but there was no history of tarry stools. At no time was there any nausea or vomiting. He consulted a physician for the first time six weeks ago and was told that the symptoms were due to a rupture. A herniorrhaphy was then done but the symptoms were not relieved. Weakness and weight loss have been quite marked; the patient has lost 37 pounds since the onset of the present illness. For the past six days there have been three to four soft, semi-liquid yellow stools daily. The patient is now eating small quantities of food but the cramp-like pains persist.

Family history is relatively unimportant except that a sister died of carcinoma of the breast. The patient is married and has six children living and in good health.

The past history is essentially negative except for the hernia operation six weeks ago. There have been no other operations or serious illnesses.

The physical examination shows little of importance except for the

abdominal findings. In the abdomen there was a hard, nodular mass in the upper right quadrant which was both visible and palpable. This mass was about the size of an orange and was thought to be in the location of the ascending colon. The liver edge was palpable two fingers breadth below the costal margin. The spleen was not palpable.

The initial impression of carcinoma of the ascending colon was based upon the orange-sized mass, the change in bowel habits, increasing constipation, a rather short history and marked weight loss. It was thought, however, that the mass was unusually large for a carcinoma of that duration, and, although exploration was indicated, further studies should be made.

Laboratory: The urine was normal at all times. The blood studies showed 3,810,000 red blood cells and a hemoglobin reading of 75 per cent, the white blood count was 11,700, of which 89 per cent were polymorphonuclear neutrophilic cells and 11 per cent were lymphocytes. The blood Wassermann and Kahn reactions were both negative. The blood chemistry findings included urea 36 and blood sugar 122 five hours postprandial. Routine isoagglutination tests were made and the blood was found to be in group four.

Roentgen examination: The chest was entirely normal. Routine film of the abdomen and urinary tract was reported as follows: "the lumbosacral region shows an osteoarthritis, otherwise normal. There are no suspicious urinary tract shadows, both kidneys are normal in size, shape, and position. There is no evidence in this examination of any localizing intestinal obstruction."

The roentgen examination of the gastro-intestinal tract was limited to the colon by means of the barium enema. The report on this examination was "large obstructing filling defect in the region of the hepatic flexure with involvement of the ascending and the proximal transverse colon. The double contrast method of examination was used following evacuation of the enema but neither barium nor air could be passed beyond the point of obstruction."

Operation: An exploratory laparotomy was done by Dr. George Crile, Jr. When the peritoneum was opened, a large mass was seen in the ascending colon just below the hepatic flexure which seemed to involve the cecum and terminal ileum. This was the size of a coconut and was soft and compressible. There were no palpable glands nor were there any palpable masses or nodules in the liver. Resection was decided to be the procedure of choice and the mass was removed without attempting to reduce the intussusception. The distal ileum was anastomosed with the transverse colon and a Witzel type of ileostomy was performed six inches proximal to the ileocolostomy. The ileostomy tube was removed in five days and convalescence was uneventful.

Pathologic report: The specimen consisted of the distal end of the ileum, cecum, appendix, and ascending colon. There was an intussusception at the ileocecal valve with about four inches of ileum extending into the invaginated cecum and ascending colon, the head of the intussusception being formed by the ileocecal valve which had an ample lumen allowing the free passage of fluid. There was marked thickening and edema of the walls of the bowel and obliteration of the lumen of the appendix. In the head of the cecum and completely surrounding the appendiceal orifice was a tumor mass about 3.5 cm. in diameter and having a slightly elevated border and a very irregular central ulcer. There were also several large, irregular ulcers in the cecum and ascending colon.

Microscopic examination of the cecum showed marked thickening of the wall, marked edema, a mild inflammatory reaction and an adenocarcinomatous growth limited to the mucosa. The final pathological report was adenocarcinoma of cecum, intussusception of cecum and ascending colon, fibrosis of the appendix and ulcerations of the cecum.

The interesting features of this case are the chronicity of the disease and the importance of differentiating the lesion from a large neoplasm. It may be seen from features of this case that, from a purely clinical point of view, the correct diagnosis of intussusception is not always easy to arrive at.

The usual case of intussusception is one with a rather short history, usually a few days or less, and with a sudden onset. The patient will have severe cramp-like pains and presents the picture of an abdominal emergency with temporary collapse and vomiting. The intestinal obstruction is usually not complete and the patient may have watery stools with visible blood or simply pass blood and mucus. Symptoms later in the course of the disease are distention, visible peristalsis, and even vomiting of intestinal material.

A comparison, then, between the usual case and the present one shows many contrasting and confusing features. The more or less gradual onset four months ago with epigastric distress certainly is not the characteristic history of an intussusception. Cramp-like pains, one of the constant findings, were present in this case but they were not especially severe. The increasing constipation becoming so marked as to require castor oil for evacuation is an important point in the history, as any change in bowel habits is always suggestive of intestinal neoplasm. In this case, however, it was due to the mechanics of the lesion and not to the small carcinoma. A mass was noted by the patient after a period of time and this had been interpreted as a hernia and operation performed without perceptible relief. Vomiting had never been present.

Intestinal carcinoma could be a justifiable clinical diagnosis in this case since many of the so-called characteristic findings of neoplastic

disease are present. In the first place the age is one period in which cancer is to be found with relative frequency. The history which the patient gives is a rather short one with a gradual onset and severity of the symptoms. Weakness and weight loss had been quite marked due, however, in the light of subsequent findings, to his inability to eat much food without pain rather than to the carcinoma. A mass was present as would be expected in a large neoplasm and this, too, showed a gradual increase in size during the course of the present illness. It is true, of course, that an adenocarcinoma was present but did not account, at least directly, for the symptoms and findings. Indirectly, the tumor may be considered a factor in the case as it may have played an important part in the formation of the actual intussusception.

The etiology of intussusception in the adult has not been entirely determined. It has been thought that tumors in the region are an important factor, since the effort on the part of the intestine to rid itself of the foreign body results in unusual peristaltic activity. The polypoid or sessile tumors would be more apt to be a contributing cause as they will be propelled into the adjoining segment of intestine and carry the bowel wall with them. Many of the reported cases of intussusception of the terminal ileum into the cecum show the presence of a lymphosarcoma of the ileum. This type of tumor was also present in the other recently examined and operated case of intussusception. In the absence of a tumor, it has been thought that a large bolus of food, or other foreign body or a relaxed bowel might be one of the contributing causes.

The diagnosis in those cases that may receive proper roentgen examination should be made with a considerable degree of accuracy. The colon examination is, of course, the method of choice, using both fluoroscopic and radiographic visualization. The most obvious finding will be the intestinal obstruction which is generally quite marked.

The appearance of the bowel at the site of the intussusception may show one of several rather characteristic pictures which, with the presence of the mass, the diagnosis may be based upon. The most typical of these will be the spiral effect as shown in figure 1 which was present in the case being presented. It will be noted in this film that the striations produced by the mucosa of the outer wall of the sheath are very clearly seen. The barium was able to pass into the space between the two intestinal walls, thus giving the most typical appearance of an intussusception. Unfortunately, however, this space cannot always be filled with the opaque enema, particularly if considerable edema is present from circulatory disturbance. In other cases, the presenting feature will be a collection of gas which remains within the barium filled bowel at the obstructed point and which is retained within the inner walls. Another often described appearance is the "cupolo" or the "pincer" effect at the distal end of the lesion. These configurations are produced by the incomplete penetra-

FIGURE 1: A characteristic appearance of an intussusception of the cecum and ascending colon. Spiral effect is produced by the presence of barium between the enclosing sheath and represents the mucosal markings of the outer bowel wall.

tion of the barium into the sheath between the two intestinal walls and will vary considerably, depending upon the amount of barium which passes into that space.

In the more acute cases it may not be possible to do a satisfactory roentgen examination with contrast media. In these, however, a plain film of the abdomen may be of considerable aid if there is sufficient gas in the intestines to show the site of the obstruction and the portions of the bowel that are dilated above the lesion.

The treatment is, in the majority of the cases, a surgical problem. In the exceptional case the intussusception will be reduced by the enema so that this procedure may at the same time serve as both a diagnostic and a therapeutic procedure.

Summary

This interesting case of intussusception has been presented to illustrate the importance of its consideration, even in what might be thought to be advanced neoplastic disease.

The roentgen examination, when the condition of the patient permits it, is the greatest single aid in making the diagnosis. Various roentgen characteristics are mentioned.